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Prognostic Predictors In Patients Submitted To Carotid Endarterectomy Under Regional Anesthesia

JULIANA PEREIRA MACEDO

TESE DE DOUTORAMENTO APRESENTADA
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PhD Programme in

Clinical And Health Services Research

of the Faculty of Medicine of the University of Porto

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Juliana Pereira Macedo

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Prognostic Predictors In Patients Submitted To Carotid Endarterectomy Under Regional Anesthesia

Preditores De Prognóstico Em Doentes Submetidos A Endarterectomia Carotídea Sob Anestesia Regional

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Since there is always another level to learn, mastery actually means you're a master of what you know and an apprentice of what you don't. We become masters of what is behind us and apprentices for what is ahead.

Gary Keller

Declaração de Integridade

Eu, Juliana Pereira Macedo, abaixo assinado, n.º mecanográfico 201400570, estudante do 3.º ano curricular do Programa Doutoral em Investigação Clínica e em Serviços da Saúde, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de investigação clínica. Declaro, sob minha honra, que atuei em conformidade com o código de ética de conduta académica da Universidade do Porto (UP), aprovado em dezembro de 2017, e com as recomendações da Comissão de Ética da UP, no desenho e elaboração do projeto de trabalho clínico e empírico, isto é, no planeamento e redação dos estudos aqui apresentados – recolha de dados, metodologia de análise, interpretação de resultados, bem como na execução do manuscrito, aprovação final e submissão.

Neste sentido, confirmo que não incorri em plágio. Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram devidamente referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, __/__/2024

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ABBREVIATIONS LIST

AI – Artificial intelligence

AMI – Acute myocardial infarction

aHR – Adjusted hazard ratio

aOR – Adjusted odds ratio

ARWMC - Age-related white matter changes

AUC – Area under the curve

BMI – Body mass index (kg/m^2)

CACC – Carotid artery cross-clamping

cCEA – Primary closure carotid endarterectomy

CEA – Carotid endarterectomy

CoW – Circle of Willis

CRT – Classification and regression tree

CS – Carotid stenosis

eCEA – Eversion carotid endarterectomy

GA – General anesthesia

GALA – General Anesthesia vs Local Anesthesia

ICA – Internal carotid artery

IND – Intraoperative neurologic deficits manifested during carotid clamping

MACE – Major adverse cardiovascular events

MICA – Myocardial infarction and cardiac arrest

MINS – Myocardial injury after non-cardiac surgery

MRA – Magnetic resonance angiography

MRI – Magnetic resonance imaging

NPV – Negative Predictive Value

NSQIP – National Surgical Quality Improvement Program

OR – Odds ratio

pCEA – Patch carotid endarterectomy

PC-MRI – Phase contrast magnetic resonance imaging

P-MR – Magnetic resonance brain perfusion tests

PSM – Propensity score matching

RA – Regional anesthesia

RCT – Randomized controlled trial

rSO2 – Regional cerebral oxygen saturation

TCAR – Transcarotid artery revascularization

TOF – Time of flight angiography

WMC – White matter changes

XGBoost – Extreme gradient boosting

ABSTRACT

ABSTRACT

Introduction

Carotid endarterectomy (CEA) is the recommended treatment for symptomatic and asymptomatic internal carotid stenosis (CS). However, the surgical intervention itself entails a risk of developing transient intraoperative neurologic deficits (IND) and other ischemic events, such as myocardial injury, that may be responsible for more severe consequences. Major complications after surgery may occur and result in combined mortality or non-fatal cardiac and stroke events that can be magnified in patients experiencing intra- and postoperative ischemic injuries.

Currently, the predictors of IND need to be well-established in the literature, and consequently, preventive strategies still need to be settled. In addition, the risk of myocardial injury after non-cardiac surgery (MINS), such as CEA under regional anesthesia (RA), is not extensively reported.

Aims

This thesis aims to clarify the predictors of IND alongside its clinical importance during CEA. Additionally, this work also aims to estimate the incidence of MINS in this subset of patients.

The first chapter of this thesis evaluates the potential of the Gupta Perioperative Myocardial Infarction and Cardiac Arrest (MICA) calculator to establish a risk stratification score for developing IND. It also focuses on identifying risk profiles and assessing the interaction between variables and their influence on the occurrence of IND. The second chapter evaluates the efficacy and practicality of employing an artificial intelligence (AI) based model to predict IND in the context of CEA, for surgical decision-

making and enhancement of patient outcomes. On the third chapter, this thesis focuses on determining whether a policy of selective shunt impacts the complication rate following CEA under RA, and to assess the 30-day stroke or Clavien-Dindo ≥ 2 rates associated with selective shunting vs. non-shunting patients. The fourth chapter of this thesis aims to assess the incidence of MINS after CEA.

Methods

To achieve the aim in the first chapter, patients undergoing CEA under RA who tested positive for IND were selected from a tertiary referral center cohort database. Consecutive CEA patients without IND were arranged in a 1:1 ratio for the control group. A classification and regression tree (CRT) algorithm was calculated, and a regressive predictive model was employed to perform a comparative analysis. Regarding the second chapter of this study, an extreme gradient-boosting predictive model was developed using machine learning and compared to a pre-existing predictive model. For interpretation purposes, a Shapley Additive exPlanations analysis was also performed.

For the third chapter's aim, all patients with IND were retrieved. Patients submitted to selective shunt were compared to a non-shunt group in a 1:1 propensity score matching (PSM) fashion. Regarding the fourth chapter, a systematic review with meta-analysis was performed to assess the incidence of MINS in CEA patients.

Results

In the first study involving 194 patients, 97 developed IND, in which obesity [adjusted odds ratio (aOR) = 4.01 (95% CI: 1.66–9.67)], higher contralateral stenosis [aOR = 1.29 (1.08–1.53)], and MICA score [aOR = 1.21 (1.03–1.43)] were determined as significant risk factors for IND occurrence. The CRT algorithm differentiated obese patients with a MICA score ≥ 8. Regarding non-obese patients, the model identified the presence of

contralateral stenosis ≥ 55% with a MICA ≥ 10. In a study of 216 patients (108 with IND), an AI-based predictive model achieved an area under the curve (AUC) of 0.82. High body mass index (BMI), contralateral stenosis and a history of limb paresis or plegia were significant risk predictors for IND during CEA. Elevated preoperative platelet and hemoglobin levels have displayed a reduced risk for IND. Another analysis, including 98 patients, showed comparable demographics and comorbidities between shunt and non-shunt groups after PSM. No significant association was found between shunt use and reduced adverse outcomes. Regarding MINS incidence in CEA patients, twenty studies with 117 933 patients were analyzed. Incidence ranged between 2% and 15.3% in patients under RA. Meta-analytical incidence of MINS was 6.3%. However, heterogeneity was superior to 99%, requiring a careful interpretation of the results.

Conclusions

Incidence of MINS is common among patients undergoing CEA. However, to minimize heterogeneity, it is essential to establish a consistent definition of MINS and employ standardized methodologies in larger cohort studies.

The AI model offers more precise IND predictions in CEA, allowing tailored interventions and improved outcomes. BMI, contralateral stenosis, and specific blood markers are key predictors, demanding validation in larger cohorts for broader clinical use. Higher preoperative platelet and hemoglobin levels are protective factors.

The MICA score has shown promising results in stratifying patients for IND in CEA, with obesity as the primary discriminator and excellent sensitivity and negative predictive value to rule out IND. Obese patients with a MICA score above 8.3 and contralateral stenosis above 55% suggest a shared profile pattern among patients who experience IND. Moreover, higher ipsilateral stenosis may help prevent procedure-related IND. Shunting

did not demonstrate advantages in reducing 30-day stroke or adverse events when compared to a non-shunting approach, warranting further investigation.

RESUMO

RESUMO

Introdução

Atualmente, a endarterectomia carotídea (CEA) é o tratamento cirúrgico recomendado para a estenose carotídea (CS) na doença sintomática e assintomática. No entanto, a intervenção cirúrgica *per se* acarreta um risco de desenvolvimento de défices neurológicos intraoperatórios transitórios (IND) e outros eventos isquémicos, como a lesão miocárdica, que podem ser responsáveis por consequências mais graves. Complicações *major* após a cirurgia podem ocorrer e resultar no *outcome* composto de mortalidade ou eventos cardíacos e cerebrais não fatais, que podem ser amplificados em doentes que sofrem lesões isquémicas intra- e pós-operatórias.

De acordo com a literatura, os fatores preditores de IND não se encontram satisfatoriamente estabelecidos e, consequentemente, as estratégias preventivas e de abordagem terapêutica permanecem em debate. Além disso, o risco de lesão miocárdica após cirurgia não cardíaca (MINS), como a CEA sob anestesia regional (RA) não está bem estabelecido.

Objetivos

A presente tese tem como objetivos clarificar os preditores de IND, bem como a sua importância clínica durante a CEA. Adicionalmente, este trabalho procura também estimar a incidência de MINS neste grupo de doentes.

O primeiro capítulo desta tese tem como objetivo avaliar a capacidade preditiva da calculadora de risco *Gupta Perioperative Myocardial Infarction and Cardiac Arrest* (MICA) em estabelecer um *score* de estratificação de risco no desenvolvimento de IND. Além disso, também se foca em avaliar a interação entre as variáveis, bem como a sua influência, no risco de ocorrência de IND. No segundo capítulo, objetiva-se avaliar a

eficácia e aplicabilidade prática de um modelo baseado em Inteligência Artificial (IA) para prever IND em contexto de CEA no processo de tomada de decisão e na otimização de resultados cirúrgicos. Relativamente ao terceiro capítulo, esta tese foca-se em determinar se uma política de *shunt* seletivo tem impacto na taxa de complicações após CEA sob RA e em determinar o risco de acidente vascular cerebral ou um *score Clavien-Dindo* ≥ 2 aos 30 dias pós-operatórios entre os doentes com *shunt* seletivo vs. sem-*shunt*. O quarto capítulo desta tese procura determinar a incidência de MINS após CEA.

Métodos

Para alcançar o primeiro objetivo do primeiro capitulo, foram selecionados doentes submetidos a CEA sob RA que testaram positivo para IND, a partir de uma base de dados de coorte de um centro de referência terciário. Paralelamente, doentes consecutivos submetidos a CEA mas sem IND foram selecionados numa proporção de 1:1 para o grupo de controlo. Um algoritmo de árvore de classificação e regressão (CRT) foi calculado e um modelo preditivo regressivo foi aplicado para comparação. Em relação ao segundo capítulo desta tese, foi desenvolvido um modelo preditivo de *Extreme Gradient-boosting* usando *machine learning* e posteriormente comparado a um modelo preditivo pré-existente. Para fins de interpretação, também foi realizada uma análise de *Shapley Additive exPlanations*. Para o objetivo do terceiro capítulo, todos os doentes que apresentaram IND foram escolhidos para análise. Os doentes nos quais um *shunt* carotídeo foi aplicado, foram comparados a um grupo sem uso de *shunt*, com recurso a um *Propensity Score Matching* (PSM) de 1:1. Por fim, para avaliar a incidência atual de MINS em pacientes submetidos a CEA no quarto capítulo desta tese, foi realizada uma revisão sistemática com meta-análise.

Resultados

No primeiro estudo, envolvendo 194 pacientes, 97 desenvolveram IND, nos quais a obesidade [*adjusted odds ratio* (aOR) = 4,01 (IC 95%: 1,66–9,67)], graus mais elevados de estenose contralateral [aOR = 1,29 (1,08–1,53)] e *score* superiores de MICA [aOR = 1,21 (1,03–1,43)] foram determinados como fatores de risco significativos para a ocorrência de IND. O algoritmo CRT diferenciou doentes obesos com uma pontuação MICA ≥ 8 para o desenvolvimento de défices. Em relação aos doentes não obesos, o modelo identificou a presença de estenose contralateral ≥ 55% com um MICA ≥ 10 como o segundo perfil que mais se associou à incidência de IND. Num outro estudo observacional com 216 pacientes (108 com IND), foi criado um modelo preditivo baseado em AI, tendo este alcançado uma *area under the curve* (AUC) de 0,82. O índice de massa corporal (BMI) elevado e os elevados graus de estenose contralateral, antecedentes pessoais de parésia ou paralisia de membros, foram identificados como preditores de risco significativos para IND durante a CEA. Adicionalmente, níveis elevados de plaquetas e hemoglobina pré-operatórios parecem assinalar um menor risco para a ocorrência de IND. Numa outra análise, incluindo 98 pacientes, as características demográficas e comorbilidades eram comparáveis entre os grupos com e sem aplicação de *shunt* carotídeo, após o PSM. Não foi encontrada associação significativa entre o uso de *shunt* e a redução de efeitos adversos. Relativamente à incidência de MINS após CEA, vinte estudos foram selecionados para análises qualitativa e quantitativa. A incidência variou entre 2% e 15,3%, sendo que após a meta-análise foi obtida uma incidência de 6,3%. Contudo, como a heterogeneidade foi superior a 99%, é necessária uma interpretação cautelosa do resultado.

Conclusão

A incidência de MINS é relativamente comum entre doentes submetidos a CEA. No entanto, para evitar maior heterogeneidade entre os estudos, é necessária uma maior consistência na definição de MINS e adotar uma metodologia mais uniforme.

O modelo de AI oferece uma previsão precisa de IND na CEA, permitindo intervenções mais personalizadas e melhores resultados. O BMI, estenose contralateral e alguns marcadores sanguíneos são preditores-chave. Valores pré-operatórios de plaquetas e hemoglobina mais elevados são fatores protetores. No entanto, é necessária uma validação em coortes maiores tendo em vista o uso clínico mais amplo.

O *score* de MICA mostrou resultados promissores na estratificação de doentes para IND na CEA, sendo a obesidade o principal discriminador e uma excelente sensibilidade e valor preditivo negativo para excluir IND. Doentes obesos com um *score* de MICA superior a 8,3 e um grau de estenose carotídea superior a 55% sugerem um perfil padrão comum entre os doentes que experienciam IND. Um grau de estenose ipsilateral mais elevado parece desempenhar um papel protetor relativamente ao risco de IND. O uso de *shunt* carotídeo não demonstrou vantagens na redução do risco de AVC ou eventos adversos aos 30 dias pós-operatórios quando comparado à abordagem sem-*shunt*, sendo necessárias mais investigações.

INTRODUCTION

INTRODUCTION

Importance and Relevance of Carotid Endarterectomy (CEA)

Stroke is the second leading cause of death in developed countries and a foremost source of long-term infirmity (1). Approximately 80% of cerebral vascular accidents manifest as ischemic strokes, with primary etiologies encompassing embolization from the internal carotid artery (ICA) or middle cerebral artery (14%), small vessel disease within the intracranial vasculature (13%), cardio-embolic sources (25%), and other cryptogenic causes (41%) (2, 3). CEA is a cornerstone in the repertory of vascular surgery, unveiling a pivotal intervention at mitigating the consequences of carotid disease. To address symptomatic carotid stenosis (CS) and higher-risk patients with asymptomatic CS degrees of 60-99% at risk of stroke, CEA plus the best medical therapy remains the recommended treatment (3). Its historical roots trace back to the year of 1954 when Dr. Eastcott and colleagues reported an incision of the carotid bulb with the end-to-end anastomosis of the ICA in a patient presenting intermittent attacks of hemiplegia, thereby marking a revolutionary landmark in vascular surgery (4). Over the years, improvements in the technique, perioperative care, and patient selection have enhanced perioperative outcomes, setting CEA status as the gold-standard treatment in preventing cerebrovascular incidents (5, 6). CEA is not only important in reducing stroke risk but also can diminish the burden of neurological infirmity and mortality, showing its crucial role in the scenery of vascular practice (5, 6).

Pathophysiology of Carotid Disease

Carotid disease, often thought of as atherosclerosis, involves a complex mix of factors that can lead to stroke and temporary episodes of reduced blood flow to the brain (7). The gradual deposits of lipids and inflammatory tissues underlie the pathophysiology within the vascular wall. Recent reports revealed a prevalence of 27.6% for an increased carotid intima-media thickness, 21.1% for carotid plaque presence, and a prevalence of 1.5% for CS in individuals ranging from 30-79 years of age (8). Studies have reported the overall prevalence of moderate (≥50%) or severe (≥70%) asymptomatic CS in numerous populations, ranging from 0.2-2.0% in females and 0.7-2.7% in males, with rates varying between those aged below 50 and those above 80 years old (9, 10). It is worth noting that after 80 years of age, prevalence rates for both males and females increase, reaching 5% for females with CS ≥ 70% degree (10). Five key components are involved in this inflammatory process: endothelial dysfunction, formation of fatty bands and atherosclerotic plaques, plaque rupture, and thrombosis (11-13). Pre-existing atherosclerotic burden is essential in the destabilization and rupture of fat plaques, leading to thromboembolic events (14). In addition, some features are associated with plaque instability, including intra-plaque hemorrhage, thinner fibrous cap, and a large fat-rich necrotic core (14-16). Plaque remodelling may be shaped by additional inflammatory cells, cytokines, and metalloproteinases (17, 18).

Surgical Modalities

The choice of surgical technique in CEA relies on the surgeon's preference, existing disease features, such as the location and the extent of obstruction, and the patient's health condition (3, 19, 20). There are several techniques used in performing CEA: primary closure technique (cCEA), eversion (eCEA), and patch carotid endarterectomy (pCEA) (3). Up to 65% of perioperative adverse events may be related to errors in surgical technique (21, 22). Sustained efforts are required to avoid perioperative events and enhance the efficiency of the procedures.

The most common approach is cCEA (primary closure), followed by eCEA (23). The primary closure method may be additionally complemented with pCEA to attempt to reduce future narrowing of the vessel by actively widening it, although heterologous material is being used to achieve this (24). Regarding eCEA, the technique is quicker than pCEA, and no prosthetic material is used (3). On the other hand, eCEA prevents the use of shunt insertion, which is a method that is occasionally employed to ensure cerebral blood flow during carotid artery cross-clamping (CACC) and is associated with higher rates of postoperative hypertension (25) and more reinterventions for hemorrhage (26). Compared to pCEA, eCEA outcomes were not statistically different regarding short-term mortality, stroke, or combined stroke and death in a meta-analysis of five randomized controlled trials (RCT) and 20 observational studies, including 16 249 eCEA and 33 251 cCEA (20). For instance, different results were observed in the meta-analysis when primary closure was considered. Relatively to observational studies, eCEA demonstrated favorable results compared to cCEA (20). However, when RCTs were taken into account, no differences were found, but lower restenosis rates favored eCEA (20).

Another systematic review of 10 RCTs (which involved 2 157 CEA procedures) compared the standard practice of using a patch with direct suturing (cCEA) of the artery (27). The analysis found that using a patch significantly lowered the overall risk of stroke both immediately after surgery and in the long-term (27). Additionally, patching also decreased the chances of artery blockage and the narrowing of the artery recurring during long-term monitoring (27). However, it is worth noting that late complications, such as prosthetic patch infections, range between 0.5 to 1% (28).

During CEA, CACC is required, although it can be responsible for hemodynamic stroke (29). Prolonged CACC time was demonstrated to augment the risk of 30-day stroke and death, with an odds ratio (OR) 1.1 for each 10-minute increase (30), as it may affect hemodynamic stability. To prevent this, although debatable, many authors suggest the application of shunt insertion, enabling continuous blood flow in the absence of adequate collateral vascularization (3, 31, 32). Shunt insertion may be used according to three policies: routine, selective, or non-shunt, according to surgeons' training and preference (3). For surgeons who employ a shunt selectively instead, the reason is that shunt insertion itself entails a perioperative stroke risk due to more extensive dissection, embolization, and poor technical expertise (33-35). However, the benefit of resorting to shunt might be questionable. Previously described predictive factors for requiring shunting during CEA include contralateral carotid occlusion (36-38) and moderate ipsilateral ICA stenosis (38), female sex, arterial hypertension, and age over 75 years (36), symptomatic presentation (37), and requiring shunting during the original procedure (39). Low-quality data from six RCTs, including 1 270 CEAs, did not allow to make any recommendations regarding shunt use (31). Similar results were found between planned shunt and non-shunt for symptomatic patients 14 days after the ischemic event index (40). Furthermore, a more extensive analysis where 28 457 CEAs (128 routine shunt, 1 740 non-shunt, and 12 489

selective shunt) were enrolled found no differences in perioperative ischemic events (41). From another point of view, in a study including 4 181 patients treated with CEA for CS, shunt insertion was associated with increased short-term stroke or death (adjusted relative risk 1.43 [95% CI, 1.05–1.95]) (42). It is not surprising that current literature concludes that the use of shunts is still controversial (3). Therefore, it is understandable that clinical practice guidelines leave this decision to the surgeon's discretion (3).

Anesthesia Approach in CEA

Currently, CEA procedures are performed using one of two types of anesthesia: regional anesthesia (RA) or general anesthesia (GA). Neither method demonstrates superiority over the other (3). The largest RCT comparing both modalities comprises 3 526 CEA patients, and no differences were reported regarding perioperative mortality, stroke, or acute myocardial infarction (AMI) (GA 4.8% vs. RA 4.5%, three events prevented per 1000 patients with RA [95% CI, -11.0–17.0]) (43). By January 2020, a meta-analysis was published, in which 31 studies with 152 376 patients who underwent CEA with RA or GA were selected for quantitative and qualitative synthesis (44). RA was found to have less morbimortality, with shorter surgical time and lower stroke, cardiac, and inpatient mortality risks. Nevertheless, when the subgroup analysis (RCTs only) was performed, no statistically significant differences were observed (44).

From a physiological perspective, performing CEA with RA, intraoperative cerebral autoregulation remains intact, leading to a reflex increase in systemic blood pressure and cerebral oxygenation following CACC (45, 46). The cerebral perfusion is maintained (43) and there is a decrease in the risk of ischemic episodes (47). However, during CEA performed under GA, this autoregulation is lost in some patients (47). With this type of

anesthesia, cerebral blood flow experiences a more significant reduction than oxygen's cerebral metabolic rate, leading to an elevated metabolism/blood flow ratio (48, 49).

A significant advantage present in patients undergoing RA is the strict neurologic monitoring, facilitating the detection of brain ischemia during CACC and shunting application, thereby preventing neurological complications (50, 51). Post-clamping intraoperative neurologic deficits (IND) incidence ranges from 7 to 30% in CEA patients under RA (52-54) and is associated with increased ischemic events (55-57). Various direct and indirect methods are employed to screen cerebral blood flow, including electroencephalography, measurement of internal carotid stump pressure, transcranial Doppler exam, continuous cerebral oxygenation through non-invasive cerebral oximetry, or somatosensory-evoked potential monitoring (58). However, the best-known diagnostic modality capable of detecting cerebral ischemia in CEA under RA remains the neurological monitoring through the awake test (3, 58-60). Despite this, at least an additional tool should be used simultaneously with neurological examination. Indeed, some patients may need conversion to GA midway through the surgery (61), and others may suffer delayed IND secondary to CACC-induced hypoperfusion (62). Another explanation relates to missed diagnosis of minor strokes in the non-dominant hemisphere, the right in most people, as it controls subtle higher functions easily unnoticed during postoperative neurologic examination (63). Near-infrared spectroscopy quantifies in real-time the regional cerebral oxygen saturation (rSO2) reflecting cerebral blood flow (64), and it is easily applied to all patients due to its non-invasive nature. A reduction of at least 20% of rSO2 on the side procedure has been described to produce a ten-fold increased risk of stroke and an eight-fold higher risk of disabling cognitive function (50). Nonetheless, the current literature has determined different optimal cut-off values (65). Some might be related to the type of equipment used, and others may be affected by sex,

brain volume, hematocrit, and skin phototype, limiting the standardization of a cut-off value (59, 66).

Clinical Indications and Patient Selection

Despite its effectiveness in reducing stroke and mortality rates among patients with CS, the invasive nature and suitability of CEA for treating patients, especially those without symptoms, have originated increasing scrutiny (3, 67-69). No surgical intervention is devoid of risks. The available evidence supports a notable risk of stroke, AMI, and death during the perioperative timing (70-72). Because of the systemic atherosclerotic burden underlying CS, this pathology often presents with other comorbidities, including coronary artery disease, chronic kidney disease, and peripheral artery disease (73-76). Published medical records suggest that a significant proportion of stroke events (approximately 40%) have additional arterial diseases affecting various territories, along with a high prevalence of other comorbidities, predisposing them to a heightened risk of experiencing secondary cardiovascular events (77, 78). It is worth noting that other possible postoperative adverse events may occur after CEA, such as cranial nerve neuropathy, bleeding, infection, and hematoma (79). For these reasons, eligibility criteria for CEA remain vital. Nonetheless, the prevalence of cerebrovascular events in adult patients with CS is up to 10-20% (80, 81). Hence, for asymptomatic and symptomatic CS, the European Society of Cardiology / European Society of Vascular Surgery and the American Heart Association/American Stroke Association guidelines have established distinct indications for invasive or conservative treatment (3, 82). Symptomatic CS above 50% are likely to benefit from carotid revascularization, whereas asymptomatic individuals may follow optimal medical therapy for CS < 60% and surgical treatment for stenosis > 60% instead

(3, 19, 83). These recommendations remain valid as long as calculated periprocedural major stroke/death rates are lower than 3% for asymptomatic individuals and inferior to 6% when symptoms are present (3). In a recent large observational study including 38 853 CEA patients, the 30-day stroke rate was 2.3% and 0.8% for mortality (71). Other studies have reported a range from 2.0-3.0% (72, 84, 85). Currently, there are no widely used tools to predict events after CEA. Li et al. have recently created a prediction machine learning XGBoost model from a cohort of 38 853 patients who underwent CEA (from the National Surgical Quality Improvement Program (NSQIP)), achieving an area under the receiver operating characteristic curve of 0.91 (95% CI, 0.90–0.92), being the symptomatic status of patients the most relevant feature of the model (71).

Current Challenges

The most concerning complication after CEA is the perioperative stroke, giving primary importance to effectively avoiding its occurrence during the procedure (86, 87). Moreover, CACC manifested as IND has been determined as a significant predictor of perioperative stroke (88). Carotid shunting has been a source of debate since shunt-related complications might cancel its advantage (89). Available data is based on studies lacking consistency in definitions, selection criteria, and sample homogeneity, due to the low incidence of IND. Standardized classifications in defining perioperative classifications and their accurate risk stratification are scarce in vascular surgery, including CEA (90). The Clavien-Dindo classification is widely used for grading perioperative complications and has been initially designed to be applied in general surgery (91), and it was further validated in urology or gynecology, demonstrating a good predictive value (92-94). This grading complications score also applies to patients undergoing CEA, making a good correlation between the grade and prognosis during follow-up (90). Clavien-Dindo classification of surgical complications involves four grades (91). Grades I and II are minor complications, whereas grades III and IV are considered major events, defined as requiring surgical, endoscopic, or radiologic intervention and life-threatening scenarios, respectively (91).

Several cardiovascular risk stratification tools, such as the Revised Cardiac Risk Index (95), the Myocardial Infarction or Cardiac Arrest (MICA) (96), and the American College of Surgeons (97) surgical risk calculators, were tailored to estimate adverse events in patients undergoing surgery, however, none of the tools were designed to predict perioperative neurologic events (98). Despite this, the American College of Surgeons surgical risk and MICA calculators have revealed an excellent capability of assessing

perioperative stroke after non-cardiac surgery (98, 99). The Gupta MICA risk calculator was developed by analyzing the most complete clinical and prospective database available – the NSQIP (96), and is currently validated as a predictor of AMI in non-cardiac vascular surgeries and major adverse cardiovascular events (MACE) after orthopedic surgery (96, 100). The included variables are the type of surgery, American Society of Anesthesiologists′ class, increased age, functional status and serum creatinine (96). Additionally, the majority of the studies emphasize IND in the setting of GA (101). The current literature is still unclear and controversial regarding the predictive factors of IND, its management, and the true benefit of the procedure in these patients.

Concerning this issue, artificial intelligence (AI) has proved its potential as a valuable predictor of outcomes in CEA (71, 102). Machine learning algorithms enable accurate prediction of ischemic events (103), identification of high-risk patients (104), and assessment of mortality risk (105). These advancements in AI-based prediction models offer opportunities for improved clinical assessment, enhancement of surgical decision-making, and tailored conduct in CEA procedures (102, 106).

The occurrence of myocardial injury after non-cardiac surgery (MINS) in CEA patients withholds a substantial damaging impact on the prognosis of the patient, namely a three-fold higher risk of MACE (107), a seventeen-fold increased risk of non-fatal AMI in vascular patients and a ten-fold higher risk of short-term death (108). This entity is defined as an important myocardial injury due to ischemia that may occur within 30 days after surgery (109). The event of MINS does not meet the classic criteria for AMI (109, 110), as the former comprises other cardiac injuries related to ischemia, excluding perioperative non-ischemic etiologies such as pulmonary embolism, cardioversion, sepsis, and others (109). The diagnostic criteria for MINS involves an isolated rising pattern of cardiac troponin values at least one value above the 99th percentile upper

reference limit of the applied measuring kit, in the absence of symptoms and electrocardiographic findings (110). In vascular surgery, one in every five patients develops MINS and it has been associated with higher mortality rates in short and long-term periods (108). Nonetheless, its true incidence has not been systematically assessed for CEA.

THESIS OVERVIEW

THESIS OVERVIEW

The present thesis aims to clarify and increase understanding of INDs' incidence and clinical importance during CEA and raise awareness of MINS.

The first chapter of this thesis exhibits the potential of The Gupta Perioperative MICA risk calculator to establish a score capable of stratifying patients based on the risk of developing IND. A classification and regression tree (CRT) algorithm was applied to find profiles of patients associated with increased risk of IND.

Regarding the second chapter of this thesis, it is applied an AI-based predictive model for IND, the Extreme Gradient Boosting (XGBoost) algorithm in a ten-fold cross-validation of 10 000 iterations to hyper-tune the parameters. An interpretive model of the predictive algorithm, SHAP (Shapley Additive exPlanations) is also presented. This model measures the contribution of each distinctive characteristic to the overall predictions. A cluster map is included to depict the data in a hierarchical context.

The third chapter focuses on the impact of carotid shunting on 30-day outcomes, such as stroke or Clavien-Dindo ≥ 2 rates, through a propensity score matching (PSM) analysis.

The fourth chapter of the thesis presents a systematic review of the incidence of MINS in CEA patients under RA and GA. A meta-analysis was also performed, even though the high heterogeneity limits the interpretation of the results.

SPECIFIC AIMS

CEA may be performed under RA and requiring CACC of the affected carotid, during which patients may develop IND resulting from cerebral hypoperfusion. Furthermore, the occurrence of IND is a predictor of perioperative stroke and no reliable tools are available in the literature to foresee its occurrence.

The occurrence of MINS after CEA significantly impacts patient morbidity, and published reports include heterogeneous samples from different vascular procedures.

Therefore, this thesis aimed to:

Chapter I

i. Evaluate the predictive capability of the NSQIP MICA risk calculator on the development of IND.
ii. Assess the influence and interactions that other variables might carry in the occurrence of IND or adverse cardiovascular events.

- Pereira-Macedo J, Lopes-Fernandes B, Duarte-Gamas L, Pereira-Neves A, Mourão J, Khairy A, Andrade JP, Marreiros A, Rocha-Neves J. **The Gupta Perioperative Risk for Myocardial Infarct or Cardiac Arrest (MICA) Calculator as an Intraoperative Neurologic Deficit Predictor in Carotid Endarterectomy.** *Journal of Clinical Medicine*. 2022 Oct 28;11(21):6367. doi: 10.3390/jcm11216367

  Impact Factor: 3.9 (2022)

  Quartile: Q1 (Scimago); Q2 (JCR)

Chapter II

i. To determine the effectiveness and feasibility of utilizing AI techniques to predict positive awake tests in carotid endarterectomy to enhance surgical decision-making and patient outcomes.

- Pereira-Macedo J., Pias AD., Duarte-Gamas L., Myrcha P., Andrade JP., António N., Marreiros A., Rocha-Neves J. **Predictive Factors Driving Positive Awake Tests in Carotid Endarterectomy Using Machine Learning**. *Annals of Vascular Surgery*. 2024 Nov 21:S0890-5096(24)00676-9. doi: 10.1016/j.avsg.2024.10.011

  Impact Factor: 1.4 (2023)

  Quartile: Q2 (Scimago); Q3 (JCR)

Chapter III

i. To determine whether a policy of selective shunt impacts the complication rate following an endarterectomy.

ii. To assess the 30-day stroke rate and additional short-term outcomes associated with selective shunting vs. non-shunting in patients where CEA is performed under regional anesthesia.

- Pereira-Macedo J, Duarte-Gamas LAF, Pereira-Neves AH, de Andrade JPAV, Rocha-Neves JMP. **Short-term outcomes after selective shunt during carotid endarterectomy: A propensity score matching analysis.** Neurocirugía. 2023. doi: 10.1016/j.neucir.2023.07.006

  Impact Factor: 0.7 (2023)

  Quartile: Q3 (Scimago); Q4 (JCR)

Chapter IV

i. To assess the incidence of MINS in patients submitted to CEA with or without regional anesthesia.

- Pereira-Macedo, J., Silva, A. F., Duarte-Gamas, L., Andrade, J. P., Sousa-Pinto, B., & Rocha-Neves, J. (2023). **Incidence of myocardial injury in patients submitted to carotid endarterectomy**. VASA. Zeitschrift fur Gefasskrankheiten, 10.1024/0301-1526/a001101. doi: 10.1024/0301-1526/a001101

  (Part of the results data was used in a Master's Degree in Medicine dissertation)

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  Quartile: Q2 (Scimago); Q3 (JCR)

CHAPTER I

PREDICTIVE CAPABILITY OF THE NSQIP MICA RISK CALCULATOR ON THE DEVELOPMENT OF INTRAOPERATIVE NEUROLOGIC DEFICITS

CHAPTER I

The predictive capability of the NSQIP MICA risk calculator on the development of IND. Improvement of patients' risk stratification for IND by delineating risk-features profiles.

Reference of the published version:

Pereira-Macedo J, Lopes-Fernandes B, Duarte-Gamas L, Pereira-Neves A, Mourão J, Khairy A, Andrade JP, Marreiros A, Rocha-Neves J. The Gupta Perioperative Risk for Myocardial Infarct or Cardiac Arrest (MICA) Calculator as an Intraoperative Neurologic Deficit Predictor in Carotid Endarterectomy. Journal of Clinical Medicine. 2022 Oct 28;11(21):6367. doi: 10.3390/jcm11216367.

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Article

The Gupta Perioperative Risk for Myocardial Infarct or Cardiac Arrest (MICA) Calculator as an Intraoperative Neurologic Deficit Predictor in Carotid Endarterectomy

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Abstract: Background: Patients undergoing carotid endarterectomy (CEA) may experiment intraoperative neurologic deficits (IND) during carotid cross-clamping. This work aimed to assess the impact of the Gupta Perioperative Myocardial Infarct or Cardiac Arrest (MICA) risk calculator in the IND. Methods: From January 2012 to April 2021, patients undergoing CEA with regional anaesthesia for carotid stenosis with IND and consecutively control operated patients without IND were selected. A regressive predictive model was created, and a receiver operating characteristic (ROC) curve was applied for comparison. A multivariable dependence analysis was conducted using a classification and regression tree (CRT) algorithm. Results: A total of 97 out of 194 included patients developed IND. Obesity showed aOR = 4.01 (95% CI: 1.66–9.67) and MICA score aOR = 1.21 (1.03–1.43). Higher contralateral stenosis showed aOR = 1.29 (1.08–1.53). The AUROC curve was 0.656. The CRT algorithm differentiated obese patients with a MICA score $\geq$ 8. Regarding non-obese patients, the model identified the presence of contralateral stenosis $\geq$ 55% with a MICA $\geq$ 10. Conclusion: MICA score might play an additional role in stratifying patients for IND in CEA. Obesity was determined as the best discrimination factor, followed by a score $\geq$ 8. A higher ipsilateral stenosis degree is suggested to have a part in avoiding procedure-related IND. Larger studies might validate the benefit of MICA score regarding the risk of IND.

Keywords: carotid endarterectomy; carotid stenosis; major adverse cardiovascular events; survival analysis; MICA score; atherosclerosis; perioperative stroke

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1. Introduction

Carotid endarterectomy (CEA) is the standard recommended surgical technique for the treatment of asymptomatic patients but especially symptomatic patients with carotid

stenosis [1,2]. A carotid stenosis of ≥50% is present in 1.5% of the population, mostly in men, representing roughly 58 million individuals worldwide [3].

The main concerns associated with this technique include perioperative embolic [4] and cerebrovascular events and myocardial infarction, which affect approximately 4% and <1% of patients, respectively [5–7].

This procedure may be executed under regional anaesthesia (RA) and requires carotid cross-clamping (CACC) of the affected carotid [4], during which a small proportion of patients manifest intraoperative neurologic deficits (IND) resulting from cerebral hypoperfusion [8]. Furthermore, the occurrence of IND has been shown to be a predictor of perioperative stroke [8].

The current literature is still unclear regarding the predictive factors of clamping intolerance. Previously, patients that manifested IND were found to have significantly higher decrement in mean flow velocity in the ipsilateral middle cerebral artery; two or more obstructions; and a reduced number of recruitable collateral vasculatures, assessed by transcranial doppler or magnetic resonance angiography (MRA) [9,10]. Recently, the use of both MRA and MRA perfusion with acetazolamide was found to carry a high sensitivity (100%) and specificity (95%) value of IND by using a calculated cut-off point of 0.322 [11]. Obesity and a higher degree of contralateral carotid stenosis were also described as independent predictors of IND [12].

The Gupta Perioperative Myocardial Infarct or Cardiac Arrest (MICA) calculator, derived from the National Surgical Quality Improvement Program (NSQIP), is a model widely used to assess the perioperative risk of intraoperative or postoperative myocardial infarction and cardiac arrest after noncardiac surgeries. This calculator is based on the type of surgery, functional status, serum creatinine, American Society of Anesthesiologists' (ASA) class, and increased age as variables [13]. The NSQIP MICA risk calculator is currently validated as a predictor of MICA in aortic or other noncardiac vascular surgeries [13] of stroke in noncardiac surgery [14], as well as an accurate discriminator of major adverse cardiovascular events (MACE) following orthopaedic surgery [15,16].

The main goal of this study was to evaluate the predictive capacity of the NSQIP MICA risk calculator on the development of intraoperative neurologic deficits (IND). In addition, this study aimed to assess the influence and interactions that other variables might carry in the occurrence of IND.

2. Material and Methods

2.1. Study Population

Patients submitted to CEA under RA between 1 January 2012 and 30 April 2021 in a tertiary referral centre presenting with IND were prospectively and consecutively included from a cohort database, and post hoc analysis was carried out. Patients in the control group were selected with a 1:1 ratio as the immediately consecutive patient submitted to CEA without the occurrence of IND.

Patients were evaluated before surgery by a vascular surgeon and an anaesthesiologist. When previously symptomatic, patients were also assessed by a neurologist. The neurologist assessed symptomatic patients to detect any persistent sequelae relevant for further comparison, which is in congruence with current management guidelines [2]. Carotid stenosis was detected and quantified by a duplex ultrasound exam or a computed tomography angiogram (NASCET), or an additional duplex ultrasound exam performed by a different independent operator. Participants were evaluated postoperatively with clinical examination and Doppler ultrasound at 30 to 90 days after discharge and at 12 months of follow-up. Other data, such as demography and comorbidities, were assessed through clinical registries. This study was reported according to STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) and Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines [17,18]. This study was approved by the University's Institutional Review Board (248-18) on 14 July 2018, and informed consent was waived by the Ethics Committee. The ongoing cohort

was registered for patient enrolment at clinicaltrials.gov (NCTNCT04347785, accessed on 3 December 2021). This study did not involve the assignment of patients to treatment groups.

2.2. Definitions

Intraoperative neurologic deficits were defined as any persistent symptomatic change or sign at neurologic awake examination (speech, motor function, and consciousness) during carotid artery cross-clamping, after hemodynamic adjustment [19]. Neuromonitoring is performed systematically to detect any subtle alteration that might be associated to cerebral ischemia, such as confusion, abrupted decrease in consciousness, or restlessness/agitation. Examples of tasks may include personal or time and space orientation questions, counting backwards, facial mimics, squeezing objects or limb mobility, direct commands from a surgeon, and assessment of consciousness level [20,21]. Event adjudication was performed by the anaesthesia–surgical team.

Carotid stenosis was considered symptomatic or asymptomatic according to the clinical practice guidelines of the European Society of Vascular Surgery [2].

Chronic kidney disease (CKD) was defined as an established diagnosis of CKD or a basal creatinine $\geq$ 1.5 mg/dL.

2.3. Surgical Technique

The surgical technique consisted of CEA followed by patch angioplasty, eversion technique, or direct suture. The choice of which approach was dictated by the intraoperative finding and the operator discretion. The surgeon also decided on the use of a carotid shunt when in the presence of IND. The centre has a reported stroke rate in CEA of 2% and a combined stroke/death rate of 2% (>100 procedures per year) [22]. Additionally, the acceptable major adverse events rate after CEA is described as 3% for asymptomatic patients and 6% for symptomatic patients, according to NSQIP Registry Carotid Endarterectomy Scale [23]. The exclusion criteria for RA are synchronous cardiac surgery and patient's a priori unwillingness to stay awake during the intervention. Intraoperative neurologic monitoring consisted of consecutive brief awake neurological examinations and surveillance every 3 min during CACC. The neurological examinations prevailed in the definition of IND events [24]. Cerebral oximeter (INVOS™) data were additionally collected. Regional anaesthesia was performed by an instituted protocol and was executed in supine position by an ipsilateral deep cervical block. A 22-gauge insulated needle was inserted under image guidance with a 90-degree angle in the majority of cases. A 4–5 mL of ropivacaine 0.5% was then administered per spinal level (C2–C4) in a total amount of 12–15 mL (deep cervical blockade), followed by/or 5 mL of ropivacaine 0.5% at the halfway posterior border of the sternocleidomastoid muscle (superficial blockade) [25].

2.4. Statistical Analysis

Statistical analysis was performed with SPSS (IBM Corp., released 2020. IBM SPSS Statistics for Windows, version 27.0, Armonk, NY, USA). For a normal continuous variable distribution, mean $\pm$ standard deviation (SD) and median (interquartile range (IQR) 25 percentile to 75 percentile) were assessed for description. For asymmetric distributions, median (IQR) calculation was preferred. Categorical variables were displayed as *n* (%) in terms of function of the dependent variable. Comparisons in univariate analysis were performed using χ^2 (or Fisher's tests, if needed) for categorical variables and Student's *t*-test or Mann–Whitney U test for continuous variables. A *p*-value inferior to 0.05 was considered as statistically significant.

NSQIP MICA risk was calculated in terms of odds of outcome, according to the available online calculator supported by the existing evidence [13,26].

For a validation study, limited evidence is available regarding the necessary sample to assess the performance of an existing model. However, current recommendations support the use of around 200 patients for validation studies [18].

The regressive predictive model was created by resorting to regression analysis and dimension reduction by the method of backward feature elimination. Variables with clinical relevance included in the multivariable analysis were associated with the group with IND in the univariate analysis with statistical significance $p < 0.1$. On the basis of clinical and MICA score predictors with statistical significance for symptomatic intraoperative cerebral hypoperfusion, two formulas were created and evaluated: a previously validated clinical predictive model [27] and a clinical plus MICA predictive model. A receiver operating characteristic (ROC) curve was applied for the comparison of both models.

To understand how some independent variables interacted with the dependent variable (IND), a tree format multivariable dependence analysis was conducted using a classification and regression tree (CRT) algorithm. This model is an adaptation of the Chi-squared Automatic Interaction Detector (CHAID) algorithm [28]. This technique was used for its ability to hierarchically rank the independent variables selected by the multivariable regression as an independent risk factor for IND (those with a $p < 0.1$) in specific algorithmic conditions (parent node = 10 cases and child node = 5 cases, in this case) by its ability to differentiate the distribution of the dependent variable, meaning the occurrence of IND, relying on the multivariable optimal binning algorithmic perspective used by the software (SPSS 27.0). Its tree-like method of result display allows for the visualisation of the variables hierarchically by the importance, degree of influence in the behaviour of the dependent variable, occurrence of IND, and determination of the optimal cut-off points, which maximises its outcome differentiation.

3. Results

3.1. Demographic and Clinical Data

The study population (n = 194) was mostly male (79.4%), with an overall mean age of 70.2 ± 9.0 years, ranging from 45 to 89 years old. Both study groups included 97 patients. A shunt was placed in 23 patients of the IND group. All the patients were under single antiplatelet (183 patients) or dual antiplatelet therapy (11 patients). No statistically significant differences were found between the IND and the control groups regarding gender (75.2% vs. 83.5%, p = 0.089), age (71.4 ± 9.2 vs. 69.0 ± 8.6, p = 0.065), or presence of cardiovascular risk factors, except for body mass index >30 kg /m^2, which was significantly more frequent in the individuals that developed IND (27.8% vs. 8.2%, $p \leq 0.001$) (Table 1).

Table 1. General patient's characteristics and preoperative comorbidities.

	Population n **= 194**	**Controls** n **= 97**	**Cases of IND** n **= 97**	p**-Value**
Gender				
Male, *n* (%)	154 (79.4)	81 (83.5)	73 (75.2)	0.089
Female, *n* (%)	40 (20.6)	16 (16.6)	24 (24.7)	
Age (years)				
Mean (±SD)	70.2 (±9.0)	69.0 (±8.6)	71.4 (±9.2)	0.065
Median (IQR)	71.5 (64–77)	71.0 (62.0–75.8)	72.0 (65.0–78.0)	
Side (right), *n* (%)	98 (50.5)	54 (55.7)	44 (45.3)	0.114
CV risk factors, *n* (%)				
Hypertension	171 (88.1)	85 (87.6)	86 (87.8)	0.865
Diabetes	82 (42.3)	38 (39.1)	44 (44.9)	0.454
Smoking history	100 (51.5)	55 (56.7)	45 (45.9)	0.113
Dyslipidaemia	166 (85.6)	82 (84.5)	84 (86.5)	0.953
BMI > 30 kg /m^2	35 (18.0)	8 (8.2)	27 (27.8)	<0.001

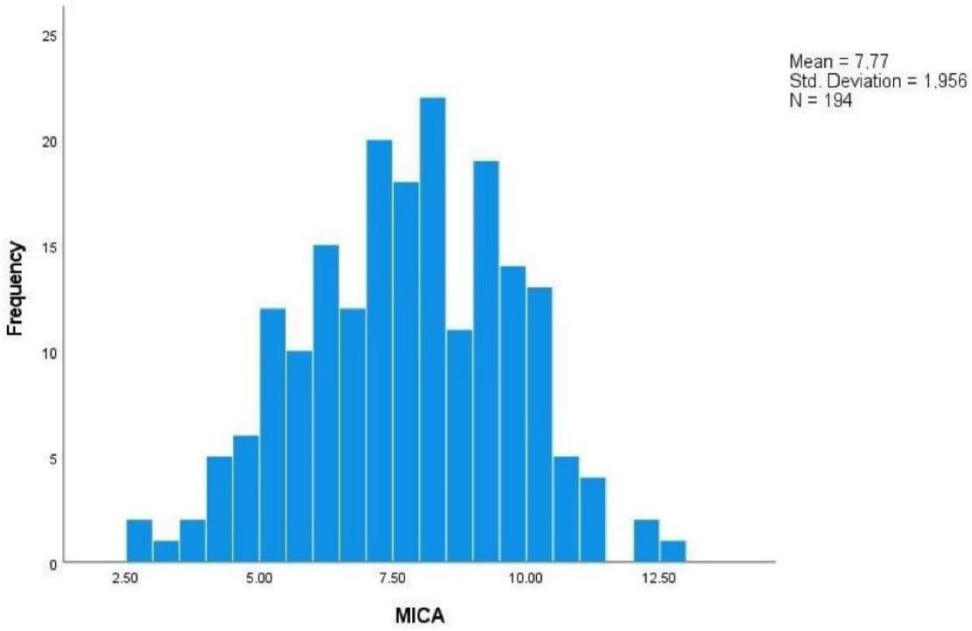
Table 1. *Cont.*

	Population $n = 194$	**Controls** $n = 97$	**Cases of IND** $n = 97$	***p*-Value**
CKD, *n* (%)	25 (12.9)	13 (13.4)	12 (12.3)	0.788
PAD, *n* (%)	47 (24.2)	25 (25.7)	22 (22.6)	0.559
CAD, *n* (%)	70 (36.1)	33 (34.0)	37 (38.1)	0.624
COPD, *n* (%)	24 (12.4)	14 (14.4)	10 (10.3)	0.354
CHF, *n* (%)	25 (12.9)	12 (12.3)	13 (13.4)	0.874
AF, *n* (%)	14 (7.3)	7 (7.2)	7 (7.2)	0.984
ASA, *n* (%)				
II	31 (16.0)	17 (17.5)	14 (14.4)	
III	150 (77.3)	74 (76.2)	76 (78.3)	0.610
IV	13 (6.7)	7 (7.2)	6 (6.1)	
Functional status, *n* (%)				
Independent	164 (84.5)	85 (87.6)	79 (1.4)	
Partially dependent	24 (12.4)	9 (9.3)	15 (15.4)	0.306
Dependent	6 (3.1)	4 (4.1)	2 (2.1)	
Asymptomatic, *n* (%)	106 (54.6)	53 (55.2)	53 (54.1)	0.875
Symptomatic, *n* (%)				
TIA	19 (9.8)	10 (10.3)	9 (9.3)	0.922
Stroke	69 (35.6)	33 (34.0)	36 (37.1)	
Stenosis degree				
Mean (±SD) (%)	83.8 ± 10.5	83.6 ± 9.6	82.1 ± 11.1	0.020
Median (IQR) (%)	80.0 (80–90)	90.0 (80–90)	70.0 (70–90)	
Contralateral stenosis degree				
Mean (±SD) (%)	63.1 ± 19.0	59.6 ± 15.2	66.6 ± 21.7	0.012
Median (IQR) (%)	50.0 (50.0–70.0)	50.0 (50.0–60.0)	60.0 (50.0–80.0)	
MICA				
Mean (±SD)	7.8 ± 2.0	7.5 ± 1.9	8.1 ± 2.0	0.032
Median (IQR)	7.8 (6.3–9.3)	7.9 (6.7–9.5)	7.7 (6.1–8.9)	

Abbreviations: 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 $\geq$ 1.5 mg/dL); COPD—chronic obstructive pulmonary disease; CV—cardiovascular; IND—intraoperative neurologic deficits; IQR—interquartile range (25–75%); MICA—Gupta Perioperative Risk for Myocardial Infarction or Cardiac Arrest; obesity—body mass index > 30 kg/m^2; PAD—peripheral artery disease; SD—standard deviation.

The degree of CEA-intervened stenosis and of contralateral stenosis were the only other two patient variables that were found to significantly differentiate the control group from the patients who suffered IND. The mean degree of contralateral stenosis was significantly higher in the case group (66.6 ± 21.7 vs. 59.6 ± 15.2, $p = 0.010$), and the degree of ipsilateral stenosis was significantly higher in the control group (83.6 ± 9.6 vs. 82.1 ± 11.1, $p = 0.020$) (Table 1).

Concerning the population's Gupta Perioperative Risk for MICA Score, it followed a normal distribution ranging from 2.7 to 12.8, with a mean score of 7.8 ± 2.0 (Figure 1, Table 1). Patients with IND showed a higher risk score, 8.1 ± 2.0, than patients in the control group, 7.5 ± 1.9 ($p = 0.032$).



Mean (SD) = 7.8 (±2.0), n = 194.

Figure 1. Histogram of the distribution of the Gupta Perioperative Risk for MICA Score. Abbreviations: MICA—Myocardial Infarction and Cardiac Arrest score; SD—Standard Deviation.

3.2. Multivariable Analysis and Confounding Variables/Factors

Included variables in the regression model were age, sex, BMI > 30 kg/m^2, ipsilateral stenosis, contralateral stenosis, and MICA score. After a multivariable regression analysis, only four of them were confirmed as independent factors for IND (Table 2). Obesity showed an aOR of 4.01 (95% CI 1.66–9.67), followed by a higher contralateral stenosis degree with an aOR of 0.69 (0.51–0.94) and MICA score with an aOR of 1.21 (1.03–1.43). Contrarily, a higher degree of ipsilateral stenosis was associated with an aOR of 0.69 (0.51–0.94).

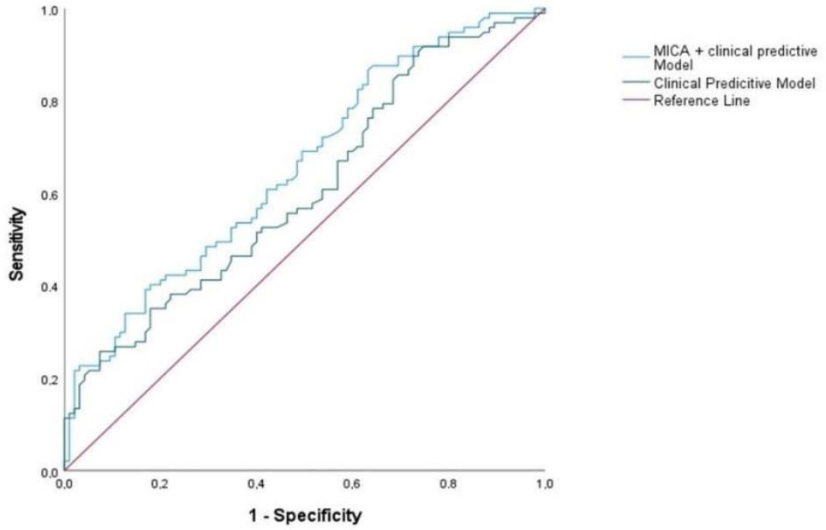
Table 2. Multivariable analysis by resorting to a regressive predictive model. Crude odds ratios (OR) and adjusted odds ratios (aOR) are displayed. The 95% confidence intervals (95% CIs) are indicated.

	Intraoperative Neurologic Deficit			
	Crude OR (95%CI)	***p*-Value**	**aOR (95%CI)**	***p*-Value**
Age	1.03 (0.99–1.06)	0.067	- *	-
Sex (female)	0.54 (0.27–1.10)	0.091	-	-
BMI > 30 kg/m^2	4.18 (1.80–9.77)	0.000	4.01 (1.66–9.67)	0.002
Ipsilateral stenosis	0.72 (0.54–0.95)	0.022	0.69 (0.51–0.94)	0.019
Contralateral stenosis	1.22 (1.04–1.44)	0.014	1.29 (1.08–1.53)	0.004
MICA score	1.18 (1.01–1.36)	0.034	1.21 (1.03–1.43)	0.019

* Excluded also due to collinearity with MICA score. Abbreviations: aOR—adjusted odds ratio; BMI—body max index; MICA—Myocardial Infarction and Cardiac Arrest Score.

3.3. The MICA Score Predictive Power

According to the calculated ROC curve analysis, the area was 0.656 (95% CI 0.580–0.732) when MICA was added to the clinical predicted model (composed of obesity and ipsilateral and contralateral stenosis degrees), which was higher (AUROC difference 0.049, $p = 0.05$), as observed in Figure 2. The optimal threshold obtained was 11.42, with a sensitivity of 87.6% and a specificity of 36.8%. Since the IND prevalence in the hospital centre is around 8%, the positive predictive value was 11%, and the NPV was 97%.



	AUROC CI 5-95%	P-value
Clinical + MICA score Predictive Model	0.656 [0.580-0.732]	<0.001
Clinical Predictive Model	0.607 [0.527–0.686]	0.011

Clinical + MICA score predictive model: (contralateral stenosis × 1.273) + (ipsilateral stenosis × 0.706) + (BMI > 30 kg/m^2 × 4.001) + (MICA score × 1.214). Clinical predictive model: includes (BMI > 30 kg/m^2 × 4.001) + (ipsilateral stenosis × 0.706) + (contralateral stenosis × 1.273) + (1.032 × age).

Figure 2. ROC curves of clinical and clinical plus MICA score models for symptomatic intraoperative neurological deficits. AUROC-area under the receiving operating characteristics; CI 5–95%: confidence interval 5–95%; MICA- Myocardial Infarction and Cardiac Arrest Score; Pseudo-R2 = 0.204-clinical plus MICA score predictive model; Pseudo-R2 = 0.188-clinical predictive model.

Additionally, as shown in Figure 3, all obese patients with a preoperative MICA score > 8.310 and with contralateral carotid stenosis > 55% developed IND, as opposed to non-obese patients, who showed a higher preoperative MICA score cut-off point (>10.820) for the same outcome in the applied classification and regression tree.

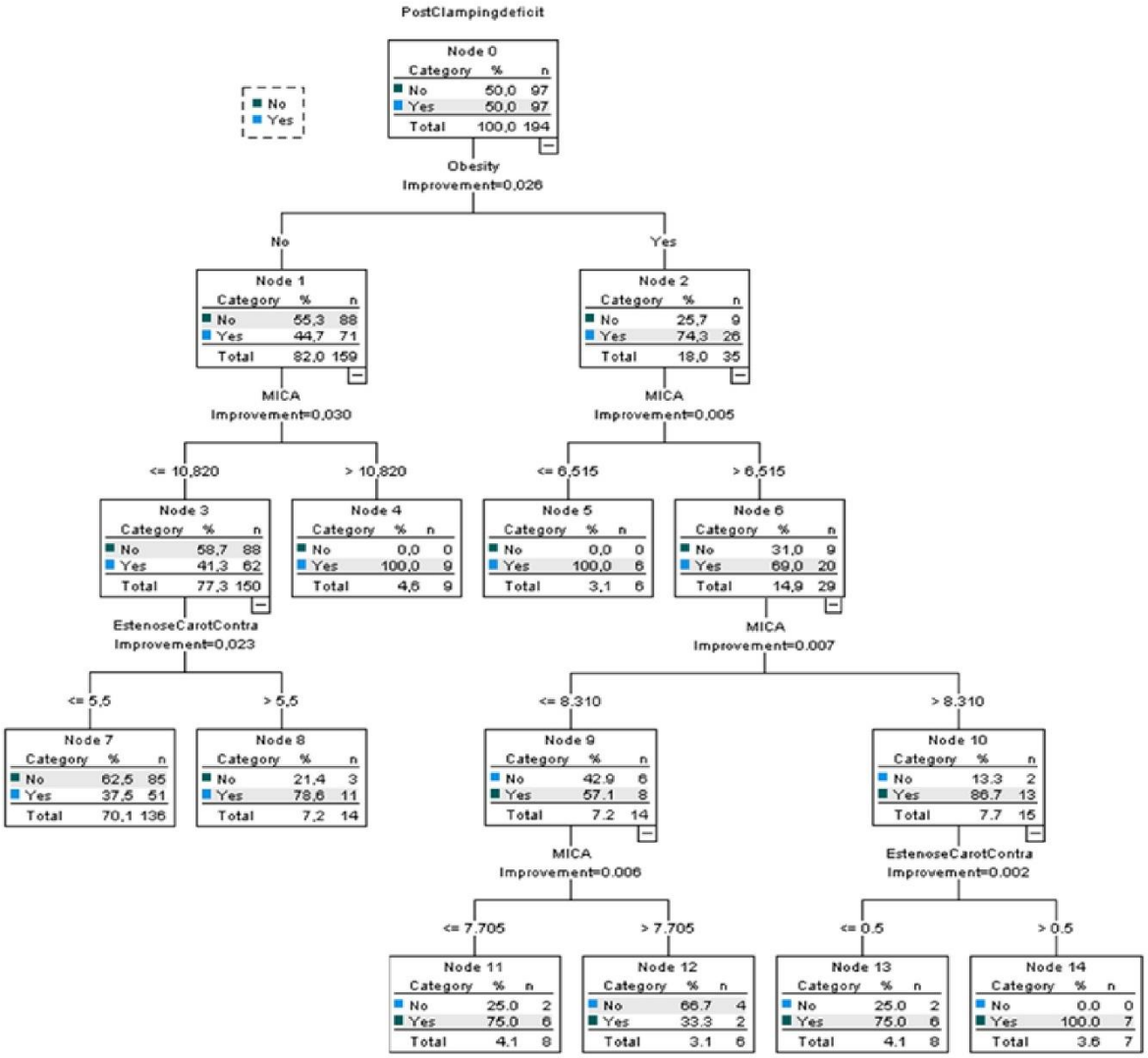


Figure 3. Classification and regression tree (CRT). The manifestation of IND was a dependent variable, while the presence or absence of a diagnosis of obesity, the degree of ipsilateral and contralateral stenosis, and the preoperative MICA score were the independent variables. Parent node = 10 cases; child node = 5 cases; maximum tree depth = 5; overall percentage = 69.1%.

4. Discussion

The benefit of predicting the occurrence of IND during CACC in CEA relies on the fact that, although being a soft surgical outcome, it is interpreted as a sign of critical cerebral ischemia and it has already been shown to predispose to hard outcomes, such as stroke or other perioperative complications [8,29].

This study primarily demonstrates that a BMI > 30 kg/m^2 is the main independent risk factor, increasing the risk of occurrence of IND in CEA by fourfold. Obesity has been associated with greater tortuosity of the extracranial internal carotid artery (OR 1.59; 95% CI, 1.35–1.86; $p < 0.001$), which may contribute to cerebral ischemia [30]. Increased risk for increased surgical time, cardiac complications, and death are also associated with obesity [31,32]. This risk is probably related to the potential these patients present for the necessity of an extensive surgical dissection and/or additional manipulation due to the higher adipose tissue content, predisposing to embolic events. The presence of obesity has

also been shown to increase the risk for carotid plaque destabilisation, contributing to the occurrence of acute cerebrovascular symptoms, particularly in males aged <70 years [33]. Factors such as a shorter neck may also contribute to a higher surgical intolerance [34].

A higher MICA risk score was demonstrated as being an independent factor for IND, with significant interaction with the remaining risk factors. In another retrospective study with 540,717 patients that underwent noncardiac surgery, MICA provided excellent results in predicting perioperative stroke, with a twofold increased risk for patients with higher scores and an overall AUC curve of 0.833 (0.825–0.842). Moreover, in this cohort, vascular surgery represented 12% of all noncardiac interventions [14]. However, MICA score was developed and validated to stratify patients according to their cardiac risk, with current evidence still lacking in terms of assessing the true impact of MICA on the occurrence of neurologic alterations [13]. Regarding the assessed AUC curve, a tendency was observed that significantly favours the applicability of adding the Gupta Perioperative MICA score over the clinical model. Age was not included individually in the ROC model because of collinearity with the MICA score, since the score already includes age itself. Furthermore, the value of the test is better perceived by its high NPV and low rate of false negatives, making it useful to rule out IND events. Still, the detected tendency may have relevance from a clinical point of view. Depending on the most frequent comorbidities or aetiology of the stenosis in the target population, it may be useful to consider the MICA score for the eligibility of the patients for CEA.

The study population also showed the presence of a higher degree of ipsilateral carotid artery stenosis as a protective factor for IND in CEA. This finding is probably explained by the increased compensatory collateral circulation from the contralateral carotid blood flow [35] and is documented in patients with unilateral carotid stenosis. This adaptation is absent in patients with bilateral stenosis, where posterior circulation is thought to compensate for the decreased brain perfusion [36]. This fact may also help to explain why a higher degree of contralateral stenosis is an independent risk factor for IND, as it compromises this adjustment. Another explanation consists in the presence of an ipsilateral hypoperfusion state in more than 80% of patients with carotid artery stenosis [37], which in chronic situations may result in the development of other adaptative mechanisms, leaving the patients with high-grade ipsilateral stenosis biologically better equipped to handle the ipsilateral CACC stress. The positive association between contralateral stenosis and the occurrence of IND has already been identified for other related outcomes, such as the increased risk of 30-day stroke/death, in-hospital strokes, and prolonged length of stay after CEA [27,38–40]. Nevertheless, it remains within the recommended guidelines, not being an absolute contraindication for surgery [27,38–40]. Having this in mind, both the presence and the degree of both ipsilateral and contralateral carotid artery stenosis are crucial during patient selection and surgical planning for CEA.

The female gender was also thought to display a higher rate of IND before the multivariable analyses but not afterward. A possible explanation may come from the low representativity of females in the sample, as a similar community-based study also showed conflicting results regarding this variable for other outcomes in CEA, with a crude incidence of indication for CEA that varied significantly by sex (female vs. male: HR 0.60 (95% CI 0.48–0.74)) but not after further adjustment for other confounding factors (female vs. male aHR 0.96 (0.76–1.22)) [41].

The use of the CRT technique allowed for the establishment of patients' profiles on the basis of the differentiating power, at various levels/generations, of the independent variables, explaining the distribution of the occurrence of IND. This technique made it possible to determine MICA score cut-off points depending on the patient's profile/generation in the CRT and added further validity to the logistic regression model. Considering this, the independent variable that primarily differentiates the occurrence or not of IND is obesity, with no influence of the independent variable contralateral carotid stenosis for non-obese individuals.

However, this work was not exempted from limitations, as this was a study with a sample size of under 200 individuals, mainly male, and from a single tertiary referral centre. Therefore, multicentre and larger sample studies are necessary to confirm and validate the present results. On the other hand, patients admitted to a tertiary referral centre are usually more endowed with significant comorbidities than those of peripheral centres, which may induce bias in interpreting results. Differences among surgical teams were also not assessed. Intraoperative hemodynamic parameters were not available and thus a correlation with the present results was not possible to establish.

5. Conclusions

MICA risk score might play some additional role in the preoperative period of CEA, stratifying patients for the occurrence of IND in CEA and consequently for worse surgical outcomes. The created predictive model with MICA has provided the ability to better rule out the event with a NPV of 97%. Additionally, obesity was shown to be the most dominant discriminating factor, followed by a MICA score above 8 points. For non-obese patients, a MICA score of 10 together with contralateral stenosis of at least 55% was also discriminative. A higher degree of ipsilateral stenosis is suggested to have a part in preventing procedure-related IND.

However, conducting further studies in carotid surgery, with larger samples, is needed to assess the real benefit of the MICA score in predicting IND and stroke. Additionally, research on the risk score for ultra-selective prophylactic shunting or other strategies to prevent and reduce the development of IND is needed to improve perioperative outcomes.

6. Key Points

Question: What is the role of the National Surgical Quality Improvement Program (NSQIP) Gupta Perioperative Myocardial Infarct or Cardiac Arrest (MICA) risk calculator in predicting the risk of intraoperative neurologic deficits in patients undergoing carotid endarterectomy?
Finding: A negative predictive value of 97% was reached and a MICA score of at least 8, together with obesity, were shown to be the two greatest discrimination factors in patients that developed intraoperative neurologic deficits.
Meaning: MICA may have a role in stratifying patients according to their probability of developing intraoperative neurologic deficits.

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Institutional Review Board Statement: This study was approved by the University's Institutional Review Board (248-18) on 14 July 2018.

Informed Consent Statement: Informed consent was waived by the Ethics Committee.

Data Availability Statement: The ongoing cohort was registered for patient enrolment at clinicaltrials.gov (NCTNCT04347785, accessed on 3 December 2021). This study did not involve assignment of patients to treatment groups.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

MICA	Gupta Perioperative Risk for Myocardial Infarction or Cardiac Arrest
NSQIP	National Surgical Quality Improvement Program
ASA	American Society of Anesthesiologists
MACE	Major adverse cardiovascular event(s)
CEA	Carotid endarterectomy
IND	Intraoperative neurologic deficits
RA	Regional anaesthesia
MRA	Magnetic resonance angiography
CACC	Carotid artery cross-clamping
CKD	Chronic kidney disease
ROC	Receiver operating characteristic
AUROC	Area under the receiver operating characteristic curve
CRT	Classification and regression tree
SD	Standard deviation
IQR	Interquartile range
BMI	Body mass index
OR	Crude odds ratio(s)
aOR	Adjusted odds ratio(s)
CI	Confidence interval
NPV	Negative predictive value
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology

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CHAPTER II

THE EFFECTIVENESS AND FEASIBILITY OF UTILIZING ARTIFICIAL INTELLIGENCE TECHNIQUES TO PREDICT POSITIVE AWAKE TESTS IN CAROTID ENDARTERECTOMY

CHAPTER II

Predictive Factors Driving Positive Awake Tests in Carotid Endarterectomy Using Machine Learning Ensemble Models

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Predictive Factors Driving Positive Awake Test in Carotid Endarterectomy Using Machine Learning

Running title: Machine Learning Predictor of Positive Awake Test

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ABSTRACT

OBJECTIVES

Positive neurologic awake testing during the carotid cross-clamping may be present in around 8% of patients undergoing carotid endarterectomy (CEA). The present work aimed to assess the accuracy of an artificial intelligence (AI)-powered risk calculator in predicting intraoperative neurologic deficits (IND).

METHODS

Data was collected from carotid interventions performed between January 2012 and January 2023 under regional anesthesia. Patients with IND were selected along with consecutive controls without IND in a case-control study design. A predictive model for IND was developed using machine learning (ML), specifically Extreme Gradient Boosting (XGBoost) model, and its performance was assessed and compared to an existing predictive model. Shapley Additive exPlanations (SHAP) analysis was employed for the model interpretation.

RESULTS

Among 216 patients, 108 experienced IND during CEA. The AI-based predictive model achieved a robust area under the curve (AUC) of 0.82, with an accuracy of 0.75, precision of 0.88, sensitivity of 0.59, and F1Score of 0.71. High body mass index (BMI) increased contralateral carotid stenosis, and a history of limb paresis or plegia were significant IND risk factors. Elevated preoperative platelet and haemoglobin levels were associated with reduced IND risk.

CONCLUSIONS

This AI model provides precise IND prediction in CEA, enabling tailored interventions for high-risk patients and ultimately improving surgical outcomes. BMI, contralateral stenosis, and selected blood parameters emerged as pivotal predictors, bringing significant advancements to

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87 decision-making in CEA procedures. Further validation in larger cohorts is essential for broader
88 clinical implementation.
89
90 Keywords: [Carotid stenosis; intraoperative neurologic deficits; perioperative stroke; regional
91 anesthesia].
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ABREVIATION LIST

AI	Artificial intelligence
AUC	Area Under the curve
BMI	Body mass index
CACC	Carotid cross-clamping
CCA	Common carotid artery
CEA	Carotid endarterectomy
CKD	Chronic kidney disease
GA	General anesthesia
IND	Intraoperative Neurologic deficits
IQR	Interquartile range
MI	Myocardial infarction
ML	Machine Learning
RA	Regional anesthesia
SD	Standard deviation
SHAP	Shapley Additive exPlanations
XGBoost	Extreme Gradient Boosting (algorithm)

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1. INTRODUCTION

Carotid endarterectomy (CEA) is a well-established and cost-effective treatment for asymptomatic or symptomatic carotid artery stenosis. Despite advancements in endovascular technique, it remains the preferred treatment option [1]. This technique is primarily done for the prevention of stroke in these patients and further being capable of reducing healthcare costs. The risk of perioperative complications, such as stroke, myocardial infarction (MI), or death, ranges from 2% to 6% [2].

During CEA, carotid artery cross-clamping (CACC) might potentially cause intraoperative neurologic deficits (IND) [3]. For every 10 minutes of increased time during arterial clamping, a higher risk of 30-day cerebrovascular and mortality events has been described, irrespective of shunt use [4]. Most intraoperative ischemic changes can be attributed to embolization, with approximately 10% associated with hemodynamic factors [5, 6]. In the event of any observed IND, timely implementation of shunting is recommended by some authors [7]. The described predictive factors in literature for IND include a body max index (BMI) superior to 30 Kg/m^2, a higher contralateral carotid stenosis degree, and a lower degree of ipsilateral stenosis [3, 8].

There is a lack of statistically significant differences in stroke, MI, and mortality rates between CEA performed under general (GA) or regional anesthesia (RA) [3, 9]. However, a major advantage of RA is that it allows continuous neurological monitoring with the awake test, which is considered the gold standard for assessing neurologic function during CACC in patients undergoing CEA [3, 10]. Several cerebral monitoring techniques, mainly described under GA, are available, such as transcranial Doppler ultrasound, electroencephalogram, stump pressure, and somatosensorial evoked potentials [6, 11, 12]. In the last network meta-analysis including almost 17 studies and 21 538 patients, although the current evidence lacks high-quality data, none of the results have shown significant differences between all monitoring tools and the awake test regarding stroke and mortality, [12]. Additionally, these methods exhibit low

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sensitivity for detecting insufficient brain blood flow and intraoperative stroke [6, 11]. It has been described that the near-infrared spectroscopy test used alone compared to the awake test may not be sensitive or specific enough to predict postoperative strokes [5].

A positive awake test is a classic indicator for shunt placement, which increases the risk of major adverse events like stroke and postoperative complications [8, 10]. Other indirectly studied risk factors for the shunting option include elderly patients above 75 years of age, symptomatic disease, and the female sex [13]. Therefore, perioperative stroke emerges as the most concerning complication following CEA, emphasizing the need for effective preventive measures during the surgery [10, 14].

Artificial intelligence (AI) has demonstrated the potential as a valuable predictor of outcomes in CEA [15]. Utilizing machine learning (ML) algorithms, AI enables accurate prediction of ischemic events [15], identification of high-risk patients [16], and assessment of mortality risk [17]. These advancements in AI-based prediction models offer opportunities for improved clinical assessment and personalized treatment in CEA procedures.

This study investigates the effectiveness and feasibility of AI techniques to predict positive awake tests in CEA to enhance surgical decision-making and patient outcomes.

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2. METHODS

This study was approved by the University's Institutional Review Board (248-18), which respects the Declaration of Helsinki, and the Ethics Committee waived informed consent. The cohort was registered for patient enrolment at clinicaltrials.gov (NCT04347785).

2.1 Study Population

Patients who underwent CEA under regional anesthesia at a tertiary referral center between January 2012 and January 2023, and who had a positive awake test, were consecutively included in the study. Patients in the control group were selected with a 1:1 ratio as the immediately consecutive patient submitted to CEA without the above-mentioned primary outcome in a case-control study design. The presence of synchronous cardiac surgery or the patient's *a priori* unwillingness to stay awake during the intervention were reasons for exclusion from the study (Figure 1). Patients with any contraindication for RA were also excluded (<1% of all patients, mostly perceived patient unwillingness). Data collection, such as demographics and comorbidities, were assessed through clinical registries. This study was reported according to the Developmental and Exploratory Clinical Investigations of DEcision support systems driven by Artificial Intelligence (DECIDE-AI) guideline [18].

2.2 Preoperative assessment

Two consecutive duplex ultrasound exams or a computed tomography angiogram were performed for carotid stenosis diagnosis.

Patients were evaluated before surgery by a vascular surgeon and an anesthesiologist. When previously symptomatic, a neurology appointment was performed. Heart rate and tensional values were measured during patient's admission to the hospital. All the patients were under

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statins, single antiplatelet (189 patients), or dual antiplatelet therapy (twenty-seven patients) before surgery.

2.3 Postoperative management

All patients were evaluated resorting to clinical examination and Doppler ultrasound at 30 to 90 days after discharge and 12 months of follow-up.

2.4 Definitions

The awake test, conducted by the anesthesiologist every three minutes during surgery, involved verbal prompts for speech (e.g. name, address), requests for limb movement, and leg tactile stimulation to assess sensory perception. A positive "awake test" (IND) was defined as any “de novo” persistent symptomatic change or sign at neurologic examination (speech, motor function, and consciousness) during CACC, after anesthesiologic therapeutic review and pharmacologic hemodynamic readjustment [19]. The anesthesia and surgery team settled the event diagnosis jointly.

Carotid stenosis was considered symptomatic or asymptomatic according to the clinical practice guidelines of the European Society of Vascular Surgery [20]. Diagnosis criteria of carotid stenosis was followed by resorting to duplex ultrasound, computed tomographic angiography and/or magnetic resonance angiography to identify and characterize the extent of the disease [20]. Chronic kidney disease (CKD) was defined as an established diagnosis of CKD or a basal creatinine $\geq$ 1.5mg/dl.

2.5 Surgical technique and anesthesia approach

The surgical technique consisted of CEA followed by patch angioplasty, eversion technique, or direct suture. The technique used depended on the choice of the operating surgeon.

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Intraoperative neurologic monitoring consisted of consecutive brief awake neurological examinations and surveillance every 3 minutes during CACC. The neurological examinations prevailed in the definition of IND events [21].

3. THEORY AND CALCULATION

3.1 Statistical Analysis

3.1.1 Bivariable analysis

The necessary sample for an Area Under the Curve (AUC) assessment was calculated resorting to online Sample Size Calculators for Designing Clinical Research (https://sample-size.net/ - aiming for AUC >80%. A total sample of 100 patients was reached. Current recommendations endorse using a minimum of 100 events and 100 non-events as it allows enough power (80%) to detect whether the predictive accuracy is different from a pre-specified null hypothesis value [22].

The bivariate analysis was performed with SPSS (IBM Corp., released 2021. IBM SPSS Statistics for Windows, version 28.0, Armonk, NY, USA). The distribution of continuous variables was assessed through skewness and kurtosis distribution tools. For a normal continuous variable distribution, mean ± standard deviation (SD) and median [interquartile range (IQR) percentile 25 - percentile 75] were assessed for description. Note that for asymmetric distributions, median [IQR] calculation was preferred. Categorical variables were displayed as n (%) in function of the dependent variable. Inferential comparisons in the bivariable analysis were performed using the chi-square test (or Fisher's tests, if conditions were violated) for both categorical variables, and Student's t test or Mann-Whitney U test, depending on normality when a variable is continuous. A P-value inferior to 0.05 was considered statistically significant.

3.2 Data understanding and preparation

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This work followed the cross-industry standard process model for data-mining [23] using Python and standard packages employed in Data Science like NumPy [24], Pandas [25], Matplotlib [26], and Seaborn [27]. Following this process model, prior to modeling, it was necessary to understand the predictive domain and the data fully. The exploratory data analysis determined that the overall quality of the data was good, with missing values in each variable below 1%. The only substantial issue was the existence of missing values in some variables, like cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), or triglycerides. The columns with more than 5% of missing values were removed from the dataset to overcome this issue. Since feature selection, particularly feature engineering contributes positively to the accuracy of prediction models [28, 29], several analyses were made to select variables, including Pearson's correlation, distribution measurement, and importance analysis in assessing several models. These operations resulted in the creation of a new variable, named ratio of the neutrophiles by the lymphocytes (ratioNeu_Lym), and the removal of several variables.

3.2.1 Modeling

ML, enables computers to learn from data, identify complex patterns, and make predictions without explicit programming. The choice of ML over other modeling options is justified by its ability to capture complex relationships among data and maintain high predictive accuracy [30].

One of the main challenges of this study was to build a ML model with a small dataset (n=216). To overcome this challenge, a cross-validation approach was employed. Cross-validation is a widely used technique for evaluating the performance of ML models, particularly when the available dataset is small. In cross-validation, the available data is divided into multiple subsets or folds. The model is then trained on all but one of these folds, and the remaining fold is used

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as a validation set to evaluate the model's performance. This process is repeated multiple times, with each fold serving as the validation set once. The results from each iteration are then averaged to produce an overall performance estimate for the model [31].

The applied modeling process involved the application of the Optuna package [32] and the Python implementation of the Extreme Gradient Boosting (XGboost) algorithm [33] in a 10-fold cross-validation of 10,000 iterations to hyper-tune the parameters to use on the fine model. XGBoost is a scalable, distributed gradient-boosted decision tree ML library [33]. This model provides parallel tree boosting and is the leading ML library for regression, classification, and ranking problems [29]. The optimal hyperparameters were identified through a "random search" approach. The score was then calculated by obtaining the best coefficient of variation, i.e., by dividing the SD of the 10-folds over the respective mean. The final XGBoost model was trained using the entire dataset, using the best 10-fold cross-validation iteration parameters (Supplemental Table 1).

To identify the drivers that allow the prediction IND, the authors employed the SHAP (Shapley Additive exPlanations) [34] model on top of the predictive model. SHAP is a game-theoretic approach to explain the output of a predictive model by measuring each feature's contribution to the model's predictions. The variables importance in predicting IND is shown by descending order, from top to bottom. A mean SHAP value representing each variable's magnitude of contribution to the occurrence of IND was displayed in a chart, where blue data points indicate that the instance has low values, while red data points indicate that the instance has high values. In addition, a heatmap representing a hierarchical clustering of data, where a color represents each patient SHAP value by feature, was also performed. The rows (patients) and columns (features) are rearranged to display similar values near each other according to the hierarchical clustering. The cluster map was created using the Seaborn package [27] and the Euclidean distance as the measure of distance.

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4. RESULTS

4.1 Demographic and clinical data

The study population (n=216) mainly was male (73.3% vs. 19.8%), with an overall mean age of 70.5 ± 8.9 years. Both groups included 108 patients, and comparison between the groups are displayed in Table 1.

Cardiovascular risk factors (Table 1) for both groups were comparable, except for obesity and triglyceride levels. Patients who experienced IND were significantly more obese than controls (30.3% vs. 9.3%, P=0.001) but had a lower mean triglyceride level (P=0.023). The mean number of antihypertensive drugs taken and patients taking beta blockers or aspirin over two weeks were also comparable between groups. Both groups were similar regarding the preoperative hematologic parameters (Table 2).

Patients with IND presented a lower degree of ipsilateral carotid stenosis (81.9% vs. 85.5%, P=0.012) but an increased contralateral stenosis degree of 66.7% (vs. 59.1%, P=0.001), as shown in Table 1. IND patients had a higher prevalence of symptomatic disease (47.2% vs. 43.0%), although this difference was not statistically significant (P=0.789).

4.2 Predictive model

The predictive model achieved an AUC of 0.82 (Figure 2), with the best Youden's index calculated at 0.5093, which was achieved at a threshold of 0.54. As presented in Supplemental Table 2, the number of False Positives (Type I error) was very low (n=9), expressing increased specificity. However, the number of False Negatives (Type II error) was relatively high (n=44). Even so, the model has reached good results, attaining 0.75 in Accuracy, 0.88 in Precision, 0.59 in Sensitivity, which resulted in an F1Score of 0.71.

The programming code of the created model can be assessed through the link https://osf.io/dx9up/?view_only=11bc2e5078c048f18036a6c37566987d.

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307 *4.3 Model's interpretation*

308 Figure 3 shows the SHAP summary plot. In the figure, each data point represents an instance.
309 The mean SHAP value by a variable is further detailed in Figure 4. High negative SHAP values
310 (on the x-axis) indicate a contribution to a lower presence of IND, while high positive SHAP
311 values indicate a contribution to a higher presence of IND. Having this in consideration, higher
312 values are seen in obesity, contralateral carotid stenosis, and preoperative limb paresis, tending
313 to carry a higher probability of resulting in IND. On the contrary, higher values of preoperative
314 platelet count, haemoglobin, and ipsilateral carotid stenosis tend to have a high probability of
315 not resulting in IND. In fact, only 10 of the 16 employed variables have some predictive power.
316 Figure 5 presents the cluster map. Besides the obvious clusters by patients based on their
317 outcome, it is possible to verify the creation of several sub-clusters.
318 If IND is not present, it is possible to observe two main sub-clusters. One of those clusters
319 presents just three observations with patients with non-obese patients but with high values of
320 contralateral stenosis. The other sub-cluster divides again into two other sub-clusters. One of
321 those is composed of obese patients. If IND is present, one sub-cluster of higher contralateral
322 stenosis is identified within patients with IND, regardless of the BMI level. Additionally,
323 another cluster of patients with IND is defined by obesity.

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5. DISCUSSION

5.1 Main findings summary and AI modeling

Using ML, it was possible to obtain a precise IND prediction in CEA achieving an AUC of 0.82. Concerning the XGBoost model, studies have demonstrated that it is a versatile ML algorithm, which excels in predicting outcomes following CEA, by simplifying complex clinical decisions [35]. It consistently outperforms alternatives like logistic regression, offering enhanced predictive accuracy with an AUC of 0.90 for 1-year stroke or death in CEA [35].

In this study, three clinical variables were associated with higher rates of IND in patients submitted to CEA under RA – obesity, higher degrees of contralateral carotid stenosis and prior contralateral limb paresis or plegia, being the former two of highest importance of contribution. On the other hand, increased levels of preoperative haemoglobin, platelets, and a higher degree of ipsilateral stenosis demonstrated to play a protective role.

5.2 Predictive factors

Obesity was the variable that contributed the most to the outcome and similar findings were previously described [3, 8, 36]. Not only is it associated with a higher prevalence of other comorbidities, but it also predisposes patients to surgical complications [37, 38] and might increase technical complexity since more adipose tissue implies more surgical manipulation and additional tissue dissection. In a large cohort study with >25000 patients submitted to CEA, metabolic syndrome was found to increase the odds of developing cardiocerebrovascular events [39]. Increased BMI has also been associated as an independent risk factor for higher degrees of tortuosity of carotid arteries, which may trigger cerebral ischemia during vascular procedures [40].

Another significant result of this work was the strong contribution of the higher degrees of contralateral carotid stenosis for IND incidence, in concordance with previous studies of the

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authors [3, 8, 36, 41]. The GALA trial advocates a similar trend between contralateral disease and cerebrovascular events, whereas perioperative stroke is extensively described in the literature [42].

In a lesser extent of magnitude, the presence of preoperative limb paresis, implying previous cerebrovascular events, is associated with a higher risk of IND [43]. This could be explained by established hemodynamic impairment due to affected middle cerebral artery velocity, with critically hypoperfused territories and compromised collateral pathways [44, 45].

5.3 Protective factors

Conversely, patients presenting a higher degree of ipsilateral carotid stenosis seem to be related to a decreased risk of IND. As previously observed in other observational studies [3, 36], this finding could be explained by the overtime development of vascular collateral pathways. Nonetheless, 80% of these patients are in a chronic state of cerebral hypoperfusion, reflecting a more resilient state when CACC is applied, especially for degrees above 90% [46, 47].

Higher haemoglobin and platelet levels were shown to display a protective role in the incidence of IND. It is known that adequate platelet level accelerates innate regenerative processes, contributing to neuronal protection [48, 49]. Pothof et al. [50] conducted a large observational study of 16068 patients submitted to CEA under GA and described a 3-fold increased risk of 30-day mortality in symptomatic patients with preoperative anemia impairing oxygenation of cells occurs during CACC. A trend to higher application of shunting was verified in anemic patients, regardless of symptomatic status. Hence, prior optimization with iron supplements or erythropoietin prescription might be beneficial [51].

5.4 Treatment strategies

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Knowing a patient's heightened risk could prompt more rigorous evaluation and discussion of alternative strategies, as the risk of stroke could reach prohibitive levels—up to 14%, questioning the potential benefits of CEA [8]. Some factors, such as haemoglobin, platelets and myocardial function, could be optimized before the intervention. A recent trial has demonstrated that targeted nutritional support might be beneficial in these patients to improve clinical and biochemical parameters to achieve better outcomes [52]. Considerations about other viable techniques without blood flow interruption and acceptable results, such as transcarotid or transfemoral revascularizations could be made [8, 53, 54].

5.5 Limitations of the study

While the present study has offered valuable insights, it is essential to acknowledge its limitations. Firstly, sample size is from a single tertiary referral center, limiting the generalization of the findings, as patients here tend to have more complex medical histories. Secondly, another important potential limitation of this study is the selection of controls in 1:1 ratio for this rare event of positive IND, which might introduce selection bias and could potentially overestimate the perceived risk of symptoms and skew the study outcomes. Additionally, differences among surgical teams such as experience and techniques were also not assessed. Another key limitation is the absence of external validation, which is crucial given the dominance of the positive class in our dataset. This limitation could impact the statistical robustness and external validity with a risk of overfitting the model.

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6. CONCLUSION

The XGBoost model achieved an AUC of 0.82, identifying key predictors of IND during CEA under RA, including higher BMI, contralateral carotid stenosis, limb paresis/plegia, and protective features, such as higher preoperative platelets and haemoglobin levels and a greater degree of ipsilateral carotid stenosis. The AI tools show promise in assisting surgeons in tailoring the best approach by identifying at-risk patients' profiles. However, further validation in larger samples is needed.

COI/Disclosures

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8. FIGURE LEGENDS

Figure 1. Flow-diagram of the study design.

CEA – Carotid Endarterectomy; CS – Carotid Stenosis; IND – Intraoperative neurologic deficits; RA – Regional Anesthesia;

Figure 2. ROC of Xgboost for intraoperative neurologic deficits during carotid endarterectomy.

Figure 3. SHAP summary plot.

PreOp erythrocytes - preoperative erythrocytes; PreOp heart rate – preoperative heart rate; PreOp paresis – preoperative paresis; PreOp platelet count – preoperative platelet count; ratioNeu_Lym - neutrophil/lymphocyte ratio; RDW-CV – red blood cell distribution width-coefficient of variation.

Figure 4. Mean SHAP value.

PreOp erythrocytes - preoperative erythrocytes; PreOp heart rate – preoperative heart rate; PreOp paresis – preoperative paresis; PreOp platelet count – preoperative platelet count; ratioNeu_Lym - neutrophil/lymphocyte ratio; RDW-CV - red blood cell distribution width-coefficient of variation.

Figure 5. Cluster map of all observations by feature's SHAP importance.

IND – intraoperative neurologic deficits; PreOp erythrocytes - preoperative erythrocytes; PreOp heart rate – preoperative heart rate; PreOp paresis – preoperative paresis; PreOp platelet count – preoperative platelet count; ratioNeu_Lym - neutrophil/lymphocyte ratio; RDW-CV - red blood cell distribution width-coefficient of variation.

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Table 1. Demographics, comorbidities and binary analysis

	Total (n=216)	**Control** (n=108)	**IND** (n=108)	***p-value***
Gender, n (%)				
Male	170 (73.3)	90 (84.1)	80 (73.4)	0.054*
Female	46 (19.8)	17 (15.9)	29 (26.6)	
Age (years)				
Mean (±SD)*	70.5 (±8.9)	69.3 (±8.60)	71.6 (±9.14)	0.054
Median (IQR)?	72.0 (14.0)	71.0 (14.0)	72.0 (13.0)	
HR, Mean (±SD)*	67.0 (±14.1)	65.6 (±11.9)	68.4 (±15.8)	0.150
Side				
Right, n (%)	104 (48.1)	58 (54.2)	46 (42.2)	0.078*
Left, n (%)	112 (51.9)	49 (45.8)	63 (57.8)	
CV risk-factors				
Hypertension, n (%)	191 (88.4)	94 (87.9)	97 (89.0)	0.793*
Diabetes, n (%)	90 (41.7)	42 (39.3)	48(44.0)	0.476*
Smoking history, n (%)	112 (51.9)	61 (57.0)	51 (46.8)	0.133*
Dyslipidemia, n (%)	188 (87.0)	92 (86.0)	96 (88.1)	0.647*
Cholesterol, Mean (±SD)	181.3 (±48.6)	182.2 (±49.4)	180.5 (±48.1)	0.706
HDL, Mean (±SD)	43.6 (±13.5)	44.4 (±14.1)	42.9 (±12.8)	0.522
LDL, Mean (±SD)	115.2 (±79.2)	119.3 (±104.1)	111.0 (±39.2)	0.254
Triglycerides, Mean (±SD)	142.7 (±66.2)	143.8 (±75.0)	141.7 (±56.2)	0.023
Obesity, n (%)	43 (19.9)	10 (9.3)	33 (30.3)	0.001*
CKD, n (%)	26 (12.0)	13 (12.1)	13 (11.9)	0.960*
Creatinine, Mean (±SD)	0.99 (±0.58)	1.01 (±0.72)	0.967 (±0.40)	0.583
PAD, n (%)	54 (25.0)	29 (27.1)	25 (22.9)	0.479*
CAD, n (%)	76 (32.1)	37 (34.6)	39 (35.8)	0.853*
COPD, n (%)	30 (13.9)	18 (16.8)	12 (11.0)	1.394*
EF <40, n (%)	27 (12.5)	12 (11.2)	15 (13.8)	0.572*
AF, n (%)	15 (7.0)	7 (6.5)	8 (7.4)	0.803*
ASA, n (%)				
II	35 (17.5)	19 (19.0)	16 (16.0)	0.742*
III	153 (76.5)	76 (76.0)	77 (77.0)	
IV	12 (6.0)	5 (5.0)	7 (7.0)	
Functional status, n (%)				
Dependent	6 (2.8)	2 (1.9)	4 (3.7)	0.238*
Partially dependent	25 (11.6)	9 (8.4)	16 (14.7)	
Independent	185 (85.6)	96 (89.7)	89 (41.7)	
Asymptomatic, n (%)	118 (54.9)	61 (57.0)	57 (52.8)	
Symptomatic, n (%)				
TIA	24 (11.2)	12 (11.2)	12 (11.1)	0.789*
Stroke	73 (34.0)	34 (31.8)	39 (36.1)	
Preoperative limb				
Plegia	55 (25.5)	20 (18.7)	35 (32.7)	0.06*
Paresis	7 (3.2)	1 (0.9)	6 (5.6)	
Stenosis degree	83.7±10.3	85.5±9.6	81.9±10.7	
Mean (±SD) (%)				0.012

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Contralateral stenosis degree				
Mean (±SD) (%)	62.9±18.6	59.1±14.7	66.7±21.1	0.001
Contralateral stenosis				
(>50%)	103 (50.7)	44 (43.6)	59 (57.8)	0.042*
(>70%)	39 (19.2)	13 (12.9)	26 (25.5)	0.023*
Anti-Hipertensive agents				
Number, Mean (±SD)	2.02 (±1.24)	2.05(±1.2)	1.99 (1.26)	0.731
Beta Blocker, n (%)	62 (31.3)	36 (36.7)	26 (26.0)	0.103*
AAS >2 weeks, n (%)	139 (65.3)	64 (61)	75 (69.4)	0.193

* - Pearson's chi-squared test

Abbreviations: AAS - Acetylsalicylic acid for more than two weeks before surgery; AF - atrial fibrillation; ASA - American Society of Anesthesiologists Physical Status Classification System; BMI - body mass index; CAD - coronary artery disease; CHF - cardiac heart failure; CKD - chronic kidney disease (creatinine 1.5 mg/dL); COPD - chronic obstructive pulmonary disease; CV - cardiovascular; EF - ejection fraction; HDL - high-density lipoprotein; HR - heart rate; IND - alterations on the neurologic examination during carotid clamping; IQR - interquartile range (25–75%); LDL - low-density lipoprotein; obesity - body mass index > 30 kg/m^2; PAD - peripheral artery disease; SD - standard deviation; TIA - transient ischemic attack.

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Table 2. Preoperative hematologic parameters

	Total (n=216)	**Control** (n=108)	**IND** (n=108)	***p-value***
Hemoglobin (g/dL)	13.2 (±1.9)	13.2 (±2.0)	13.2 (±1.8)	0.314*
MCHC (g/dL)	33.7 (±1.2)	33.9 (±1.1)	33.6 (±1.2)	0.504*
RDW-CV (%)	13.57 (±1.3)	13.3 (1.2)	13.3 (1.7)	0.065*
RDW-SD (fL)	44.3 (±4.5)	43.5 (4.9)	43.8 (4.1)	0.870*
Lymphocyte count	2.0 (±0.7)	2.1 (±0.7)	1.9 (±0.7)	0.797*
Lymphocyte (%)	27.7 (±8.8)	28.7 (±9.0)	26.7 (±8.5)	0.545*
Neutrophil count	4.5 (2.1)	4.3 (1.8)	4.5 (2.2)	0.423¤
Neutrophil (%)	60.6 (±9.9)	59.5 (±10.0)	61.7 (±9.8)	0.666*
Platelet count	211.0 (83.0)	206.5 (86.0)	213.0 (82.5)	0.819¤
MPV (fL)	11.0 (±0.9)	10.9 (±0.96)	11.0 (±0.91)	0.145*
PDW (fL)	13.3 (±2.3)	12.9 (2.73)	13.0 (2.8)	0.615¤
Neutrophil/lymphocyte ratio	2.3 (1.6)	2.1 (1.6)	2.3 (1.5)	0.109¤
Platelet/lymphocyte ratio	113.4 (69.3)	101.1 (71.9)	114.2 (65.5)	0.084¤
Haemoglobin/platelet ratio	0.1 (±0.0)	0.1 (±0.0)	0.1 (±0.0)	0.489
PDW / platelet ratio (fL)	0.06 (0.0)	0.1 (0.0)	0.1 (0.0)	0.778¤
RDW-CV / platelet ratio (%)	13.3 (3.1)	6.3 (2.3)	6.3 (3.2)	0.769¤

* – T-test; ¤ - Mann–Whitney U test;
IND – neurologic deficits; MCHC - mean corpuscular hemoglobin concentration; MPV - mean platelet volume; PDW - platelet distribution width; RDW-CV - red blood cell distribution width-coefficient of variation; RDW-SD - red blood cell distribution width - standard deviation.

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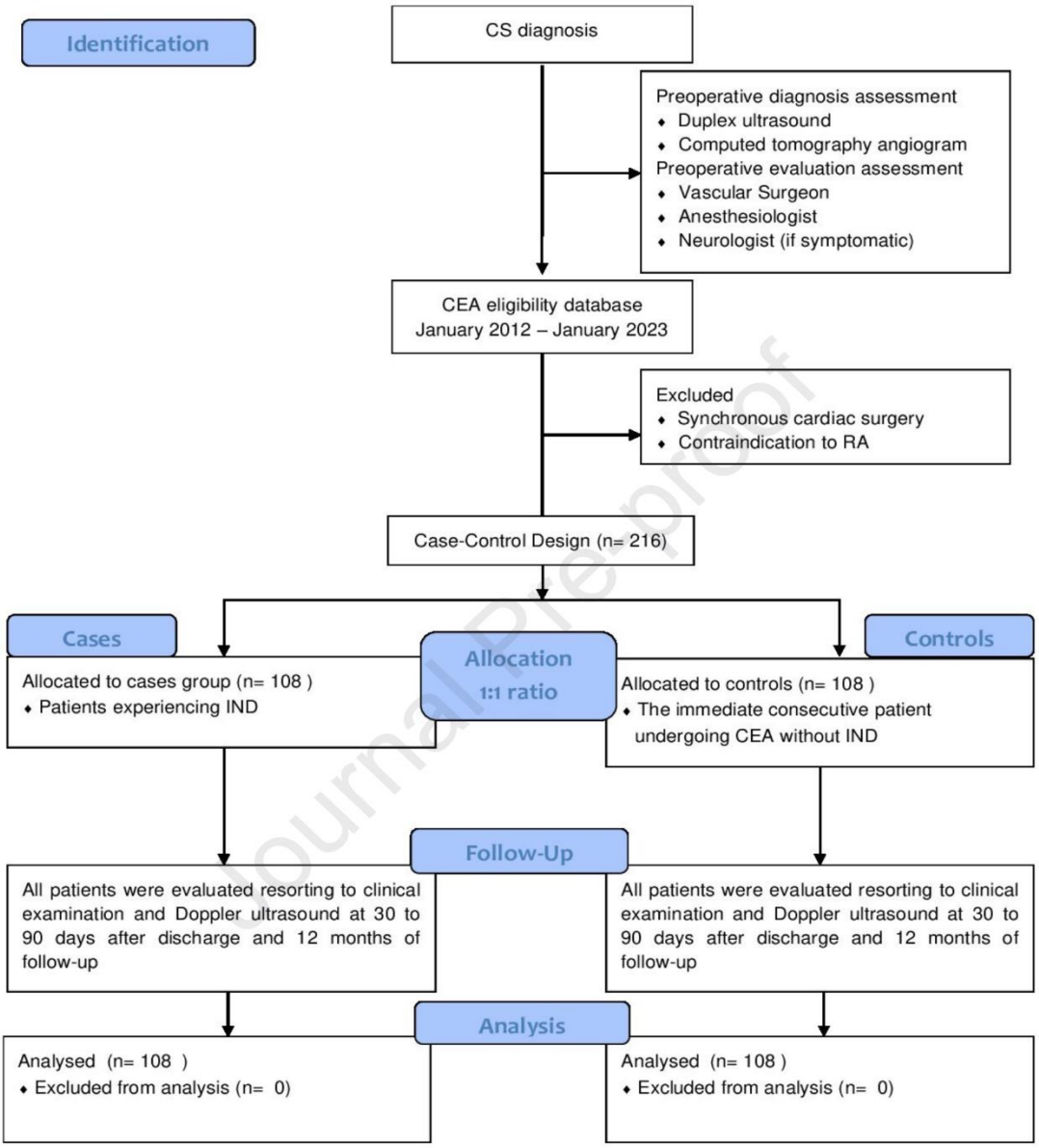

Figure 1 – ROC of Xgboost for intraoperative neurologic deficits during carotid endarterectomy.

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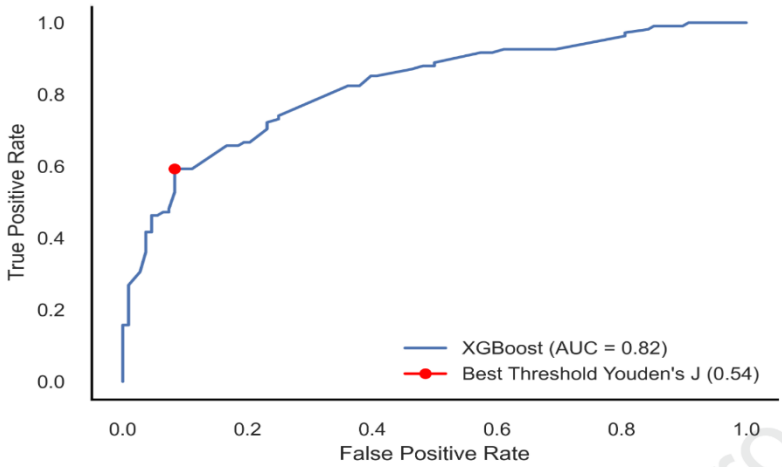

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Figure 2 – SHAP summary plot. Each data point represents an instance .

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Abbreviations: PreOp erythrocytes - preoperative erythrocytes; PreOp heart rate – preoperative heart rate; PreOp paresis – preoperative paresis; PreOp platelet count – preoperative platelet count; ratioNeu_Lym - neutrophil/lymphocyte ratio; RDW-CV – red blood cell distribution width-coefficient of variation.

Figure 3 – Mean SHAP value by variable.

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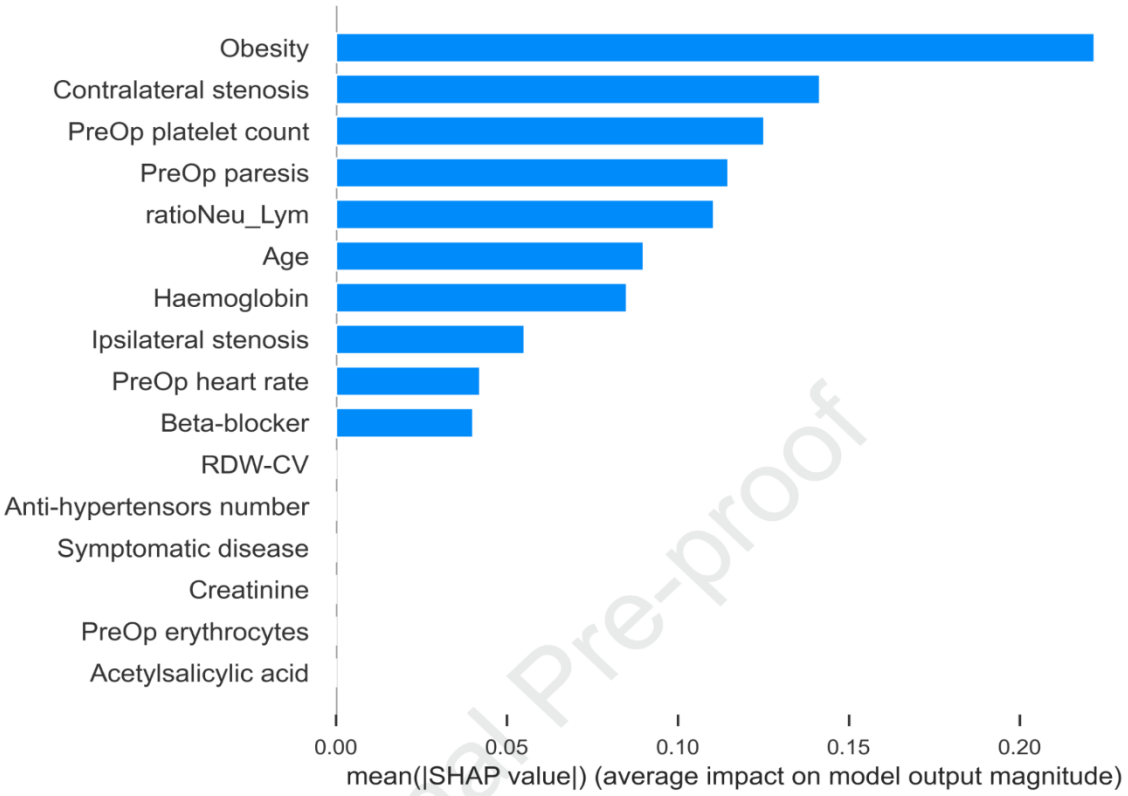

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Abbreviations: PreOp erythrocytes - preoperative erythrocytes; PreOp heart rate – preoperative heart rate; PreOp paresis – preoperative paresis; PreOp platelet count – preoperative platelet count; ratioNeu_Lym - neutrophil/lymphocyte ratio; RDW-CV - red blood cell distribution width-coefficient of variation.

Figure 4 – Cluster map of all observations by feature's SHAP importance.

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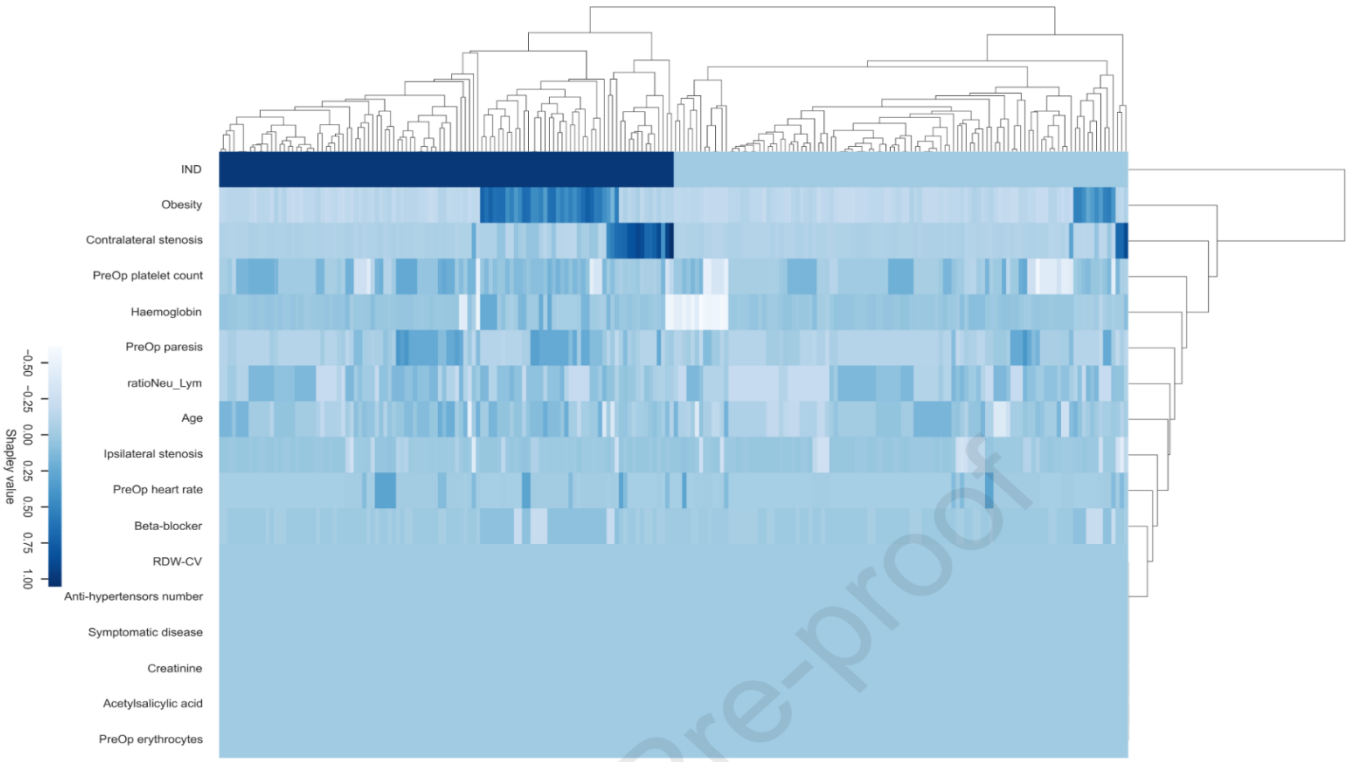

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Abbreviations: IND – intraoperative neurologic deficits; PreOp erythrocytes - preoperative erythrocytes; PreOp heart rate – preoperative heart rate; PreOp paresis – preoperative paresis; PreOp platelet count – preoperative platelet count; ratioNeu_Lym - neutrophil/lymphocyte ratio; RDW-CV – red blood cell distribution width-coefficient of variation.

CHAPTER III

THE IMPACT OF SELECTIVE CAROTID SHUNTING ON THE COMPLICATION RATES FOLLOWING AN ENDARTERECTOMY UNDER REGIONAL ANESTHESIA

CHAPTER III

Impact of selective carotid shunting on complication rates after CEA under RA

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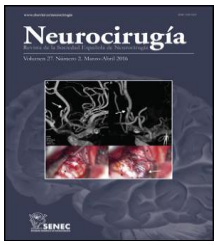

Clinical Research

Short-term outcomes after selective shunt during carotid endarterectomy: a propensity score matching analysis☆

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ABSTRACT

Introduction and objectives: Carotid cross-clamping during carotid endarterectomy might lead to intraoperative neurologic deficits, increasing stroke/death risk. If deficits are detected, carotid shunting has been recommended to reduce the risk of stroke. However, shunting may sustain a specific chance of embolic events and subsequently incurring harm. Current evidence is still questionable regarding its clear benefit. The aim is to determine whether a policy of selective shunt impacts the complication rate following an endarterectomy.
Material and methods: From January 2013 to May 2021, all patients undergoing carotid endarterectomy under regional anesthesia with intraoperative neurologic alteration were retrieved. Patients submitted to selective shunt were compared to a non-shunt group. A 1:1 propensity score matching (PSM) was performed. Differences between the groups and clinical outcomes were calculated, resorting to univariate analysis.
Results: Ninety-eight patients were selected, from which 23 were operated on using a shunt. After PSM, 22 non-shunt patients were compared to 22 matched shunted patients. Concerning demographics and comorbidities, both groups were comparable to pre and post-PSM, except for chronic heart failure, which was more prevalent in shunted patients (26.1%, $P = 0.036$) in pre-PSM analysis. Regarding 30-day stroke and score Clavien–Dindo ≥ 2, no significant association was found ($P = 0.730$, $P = 0.635$ and $P = 0.942$, $P = 0.472$, correspondingly, for pre and post-PSM).

☆ This work was developed at Centro Hospitalar Universitario de São João do Porto, Department of Angiology and Vascular Surgery.

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Conclusions: In this cohort, resorting to shunting did not demonstrate an advantage regarding 30-day stroke or a Clavien–Dindo ≥ 2 rates. Nevertheless, additional more extensive studies are mandatory to achieve precise results concerning the accurate utility of carotid shunting in this subset of patients under regional anesthesia.

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Palabras clave:
Derivación carotídea
Derivación selectiva
Déficits neurológicos intraoperatorios
Hipoperfusión cerebral
Pinzamiento carotídeo
Anestesia regional

Resultados a corto plazo después de shunting selectivo durante la endarterectomía carotídea con anestesia regional: un análisis de propensity score-matching

R E S U M E N

Introducción y objetivos: El pinzamiento carotídeo durante la endarterectomía carotídea podría provocar déficits neurológicos intraoperatorios, lo que aumenta el riesgo de accidente cerebrovascular/muerte. Si se detectan déficits, se ha recomendado la derivación carotídea para reducir el riesgo de accidente cerebrovascular. Sin embargo, la derivación puede sostener una posibilidad específica de eventos embólicos y, posteriormente, provocar daños. La evidencia actual aún es cuestionable con respecto a su claro beneficio. El objetivo es determinar si una política de derivación selectiva afecta la tasa de complicaciones después de una endarterectomía.

Material y métodos: Desde enero de 2013 hasta mayo de 2021 se recuperaron todos los pacientes sometidos a endarterectomía carotídea bajo anestesia regional con alteración neurológica intraoperatoria. Los pacientes sometidos a derivación selectiva se compararon con un grupo sin derivación. Se realizó una coincidencia de puntuación de propensión (PSM) 1:1. Se calcularon las diferencias entre los grupos y los resultados clínicos recurriendo al análisis univariado.

Resultados: Se seleccionaron 98 pacientes, de los cuales 23 fueron intervenidos mediante derivación. Después de la PSM, se compararon 22 pacientes sin derivación con 22 pacientes emparejados con derivación. Con respecto a la demografía y las comorbilidades, ambos grupos fueron comparables a los de antes y después de la PSM, excepto por la insuficiencia cardíaca crónica, que fue más prevalente en los pacientes con derivación (26,1 %, P = 0,036) en el análisis previo a la PSM. En cuanto al accidente cerebrovascular a los 30 días y la puntuación de Clavien–Dindo ≥2, no se encontró asociación significativa (P = 0,730, P = 0,635 y P = 0,942, P = 0,472, correspondientemente, para pre y post-PSM).

Conclusiones: En esta cohorte, recurrir a la derivación no demostró una ventaja con respecto a las tasas de ictus a los 30 días o Clavien–Dindo ≥ 2. Sin embargo, se requieren estudios adicionales más extensos para lograr resultados precisos sobre la utilidad precisa de la derivación carotídea en este subgrupo de pacientes bajo anestesia regional.

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Introduction

Periprocedural stroke in carotid endarterectomy (CEA) setting remains a challenge to be addressed. Indeed, CEA demands intraoperative carotid cross-clamping (CACC), which might induce neurologic deficits and promotes death by predisposing patients to cerebral hypoperfusion or embolic events.[1–3] Embolic stroke during the procedure has been significantly reduced by dual antiplatelet therapy.[2] Clinicians who support routine shunting believe that it lowers the risk of cerebral hypoperfusion and hemodynamic stroke. Other surgeons manifest against shunting or are more selective in its use, claiming that shunting itself entails a stroke risk which makes its use controversial.[4,5] due to dissection, embolization, or poor technical execution.[6] Therefore, the carotid shunting strategy is commonly recommended in patients presenting intraoperative neurologic deficits (IND) as it might reduce the risk of perioperative stroke due to the temporary interruption of cerebral blood flow.[7] However, a positive awake test is defined as any consistent change found at neurologic tests performed during CACC and that is resistant to hemodynamic adjustment.[8,9] In addition, this method is considered the most reliable to monitor cerebral ischemia.[10]

Since current evidence is still scarce and inconclusive, this study aims to assess the 30-day stroke rate and additional

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short-term outcomes associated with selective shunting vs. non-shunting in patients where CEA is performed under RA.

Materials and methods

This study was reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.[11] The study protocol (248-18) was approved by the Ethics Committee and respected the Declaration of Helsinki.

Study sample

This was a prospective single-center recruiting patients from January 2013 to May 2021. All patients from a tertiary university hospital submitted to CEA under RA with a positive awake test were included. Patients submitted to shunting were selected as the exposure group, whereas non-shunting patients were chosen as the non-exposure set.

Symptomatic carotid stenosis was defined following the current guidelines of the European Society for Vascular Surgery. It remained unchanged since the start of the recruitment.[12] Patients were evaluated before surgery, and when previously symptomatic, patients were also assessed by a neurologist or internist. No patients submitted to cerebral revascularization techniques were present in this study (Ex: Thrombolysis and Thrombectomy). A senior neurologist assisted all postoperative strokes.

Both groups were analyzed, and 30-day outcomes, such as stroke, mortality, and complication score Clavien–Dindo $\geq$2, were assessed.[13,14] In the inpatient setting, recorded adverse outcomes in this study included surgical hematoma, hypotension with the need for aminergic support, and hyperperfusion syndrome. The incidence of restenosis was also evaluated at three months. Additionally, both groups were compared in terms of age, sex, hematologic parameters, existing comorbidities, and surgical strategies.

Before CEA, the whole sample was submitted to complementary examinations, such as two Doppler ultrasounds and/or computed tomography (CT) angiography, to stratify all the carotid lesions and define the cerebrovascular topography and intrinsic disease.[15]

Before surgery, all patients were under the best medical treatment (>95% were under single anti-platelet therapy and statin).

Data availability

This trial is registered on the ClinicalTrial.gov public website with the identifier NCT04347785.

Surgical technique and anesthetic approach

All patients in this cohort underwent CEA procedures under RA by the intermediate cervical blockade. Based on surgeons' discretion, CEA consisted of direct suture, eversion, or applied patch angioplasty. More than 98% of the CEA are performed under RA in this referral center. The involved vascular department has reported rates of stroke and death after CEA, 1.10% and 0.6% in symptomatic patients, respectively.[16,17]

Neurologic examination was performed immediately after the cervical blockade and every 5 min after CACC. It was considered the test that prevailed in decision-making. At the beginning of the year 2013, a cerebral oximeter (INVOS^{TM}, Medtronic plc) for complementary monitoring was additionally applied.[18,19] If any neurologic alteration was identified after CACC and persisted after hemodynamic adjustment, a positive awake test was present, and the option to shunt was considered. Mean arterial pressure (MAP) was measured invasively using a 20-gauge catheter placed in the radial artery. Until the carotid artery was decamped, mean arterial pressure was kept between baseline values of 20% and above. If required, vasoactive medication was administered to increase MAP (ephedrine 5–10 mg bolus for hypotension and atropine 1 mg bolus for bradycardia). This center used the Javid shunt until 2015, and to this day, the Pruitt-Inahara shunt has been the choice. In the remaining cases that presented alterations, the preferred method of the surgical team was to haste the procedure with a direct closure approach.

Follow-up was implemented in the outpatient clinic's subsequent 30 and 90 days. Doppler ultrasonography and clinical examination were performed on all patients.

Other definitions

A Clavien–Dindo classification superior to 2 was defined as any required pharmacological treatment (excluding antiemetics, antipyretics, analgesics, diuretics, and electrolytes), blood transfusion, or total parenteral nutrition to address surgical complications.[20,21] Posterior circulation disease was defined by the presence of vertebral artery stenosis with hemodynamic impact, such as peak systolic velocity >90 cm/s on ultrasound or above 50% in the CT-angiography in any basilar circulation.[22,23]

Awake neurologic examination is a standardized evaluation that was applied every 10 min during the procedure, and after carotid clamping, the assessment time was reduced to every 5 min.[24]

Statistical analysis

SPSS 27.0 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp) was used to perform statistical analysis.

Baseline characteristics are presented as mean $\pm$ standard deviation (SD) values or median with interquartile range (IQR) values for continuous variables or as numbers with percentages for categorical variables, respectively.

Independent samples Student's T-test was performed for univariate analysis with continuous variables and χ^2 for dichotomous variables. Skewed variables were approached by resorting to non-parametric sign tests for related samples.

A regressive predictive model was created using the dimension reduction method of backward feature elimination. Variables with clinical relevance included in the multivariable analysis were selected using the univariate analysis with statistical significance $P < 0.1$.

To reduce selection bias between the two groups, a Propensity Score Matching (PSM) was performed. In this procedure, pairs of patients were established using 1:1 matching with a $\pm$

0.05 caliper without replacement. The standardized mean differences were calculated to compare patient features before and after matching, and the imbalance was defined as an absolute value greater than 0.20. Student's paired sample T-test and McNemar were performed concerning continuous and categorical variables, respectively.

All tests were two-tailed, and a P-value <0.05 was considered a statistically significant result.

Results

Population analysis

A total of 98 patients submitted to CEA under RA who presented IND were selected, whereas shunting was used in 23 of them. This last set of patients was compared to a non-shunt group of 75 patients. Both groups were comparable regarding age (shunt 70.5 ± 9.62 vs. non-shunt 71.6 ± 9.15, P = 0.614). Most patients were male, and there were no significant differences between shunt and non-shunt groups (P = 0.942) (Table 1).

Concerning pre-existing comorbidities, the prevalence of chronic heart failure with reduced ejection fraction was significantly higher in patients whose shunt was performed (26.1% vs. 9.3%, P = 0.038) and confirmed by multivariable analysis [adjusted Odds Ratio (aOR): 3.4 95% CI: 1.01–11.53, P = 0.047]. Other baseline characteristics did not demonstrate statistically significant differences, as observed in Table I, and were not confirmed by multivariable analysis. Hematologic parameters were also compared between the groups, and assessed P-values were >0.05. The variables examined reported <1% missing data.

Nonetheless, when PSM was applied in the sample, no statistically significant differences were found between the groups regarding demographics and inherent baseline comorbidities (Table 1, Fig.1). Furthermore, regarding demographics and patients' comorbidities, any imbalances superior to 0.20 were detected.

Intraoperative setting

CACC time was higher in the exposure group (45.4 ± 22.42 min), but the difference was not statistically significant (P = 0.784) (Table 2). Eleven patients were converted to general anesthesia, four of whom were submitted to shunt.

Follow-up at 30-days after CEA

Concerning short-term adverse outcomes, no benefit regarding resource to shunt and 30-day stroke or a Clavien–Dindo ≥ two could be statistically established (20.0% vs. 80.0%, P = 0.730 and 24.0% vs. 76.0%, P = 0.942, respectively) (Table 3). Only a small portion (13%) of the strokes were related to conversion to general anesthesia, but the association was not significant. Likewise, shorter or longer clamping times did not show statistically significant results (P = 0.508 and P = 0.250, respectively). Similar findings were found when PSM was performed (Table 2).

Follow-up at 90-days after CEA

When assessing further restenosis of 50% and 70%, no significant findings were found between the shunt and the non-shunt group (P = 0.762). Of the 18 patients interventioned with shunt, 16.7% had further restenosis of at least 50%, comparing with 13.8% (n = 8) of the non-shunt group.

Discussion

The main findings of this study support that the decision to shunt might not play a substantial role in protecting patients regarding potential postoperative adverse events, although the results of the present study cannot exclude its benefit. Incidence of stroke or a complication score classified as Clavien–Dindo ≥ 2 in patients submitted to shunting did not present statistical significance compared to the control group.

The National Surgical Quality Improvement Programme (NSQIP) database suggested that shunting had no association with perioperative stroke or death (P = 0.34). This analysis included more than 3800 patients undergoing CEA, with 87% of them under general anesthesia (vs. RA, P = 0.55 regarding stroke/death outcome).[25] In another study, 7.4% of patients (n = 1212) submitted to CEA with RA, and shunting did not impact short-term morbidity or mortality.[26] Additionally, the authors have found that contralateral carotid occlusion and severe kidney disease were independent predictors of the need for carotid shunting, with five and two-fold increased risks, respectively.[27]

In the pre-PSM analysis, the patch with shunt technique has shown lower rates of a Clavien–Dindo 2, when compared to direct suture or eversion. However, none of these differences were confirmed after PSM was performed, and no association can be inferred. Patients that were submitted to eversion and direct suture procedures belonged to the non-shunt group. No significant association was observed when both exposure and non-exposure were compared regarding 30-day stroke. In a recent retrospective cohort of 653 patients undergoing CEA for symptomatic carotid stenosis, the use of a selective shunt could not validate its benefit in reducing perioperative major adverse cardiac events (MACE). However, all patients were submitted to general anesthesia.[27]

The reasoning for the present study is the assumption that patients developing neurologic deficits (ND) during CACC have a higher risk of developing a perioperative stroke. Some ischemic lesions are associated with injury to the ischemic penumbra surrounding recent infarction and the traditional association between procedure-related embolization and intra- and postoperative stroke.[28] Before uninterrupted flow in the carotid shunt is guaranteed, the ipsilateral hemisphere is hypoperfused, thus compromising blood flow and potentially leading to local thrombosis or direct neuronal lesion.[29] Excellent results were documented in several large clinical series; for example, in a meta-analysis by AbuRahma et al., they studied up to 12,032 patients using a shunt, with perioperative stroke rates in the range of 0.7%–3.6%.[7] On the other hand, surgeons who refute its use back their option with several reports stating that shunting might be dispensable in

Table 1 – Demographics and characteristics of patients.

	Before PSM		After PSM		
	Non-shunt n = 75	Shunt n = 23	Non-shunt n = 22	Shunt n = 22	P-value
Sex (male), n (%)	56 (74.7)	17 (73.9)	17 (77.3)	16 (72.7)	0.728
Age, mean ± SD	71.6 ± 9.15	70.5 ± 9.62	69.6 ± 10.17	70.5 ± 9.85	0.784
Side (left), n (%)	41 (54.7)	13 (56.5)	15 (68.2)	12 (54.5)	0.353
CV risk factors, n (%)					
Hypertension (%)	65 (86.7)	21 (91.3)	19 (86.4)	20 (90.9)	0.635
Diabetes (%)	33 (44.0)	11 (47.8)	11 (50.0)	10 (45.5)	0.763
Dyslipidemia (%)	64 (85.3)	20 (87.0)	20 (90.9)	19 (86.4)	0.635
Smoking (%)	37 (49.3)	8 (34.8)	11 (50.0)	8 (36.4)	0.361
BMI > 30 kg/m^2 (%)	20 (26.7)	7 (30.4)	6 (27.3)	7 (31.8)	0.741
CKD (%)	10 (13.3)	2 (8.7)	5 (22.7)	1 (4.5)	0.079
COPD (%)	9 (12.0)	1 (4.3)	2 (9.1)	1 (4.5)	0.550
CAD (%)	25 (33.3)	12 (52.2)	10 (45.5)	12 (54.5)	0.546
PAD (%)	14 (18.7)	8 (34.8)	6 (27.3)	8 (36.4)	0.517
FA (%)	5 (6.7)	2 (8.7)	3 (13.6)	2 (9.1)	0.635
CHF (%)	7 (9.3)	6 (26.1)	4 (18.2)	6 (27.3)	0.472
Symptomatic (%)	31 (41.9)	9 (39.1)	10 (45.5)	6 (27.3)	0.210
TIA (%)	6 (10.8)	3 (12.9)	2 (9.1)	1 (4.5)	
Stroke (%)	29 (29.9)	6 (26.1)	8 (36.4)	5 (22.7)	
Stenosis degree, mean ± SD (%)	81.3 ± 11.7	84.5 ± 8.6	83.2 ± 8.9	84.5 ± 8.6	0.608
Contrateral stenosis degree, mean ± SD (%)	65.8 ± 21.2	69.5 ± 23.2	72.7 ± 22.7	69.5 ± 23.2	0.648
Posterior circulation disease, n (%)	15 (24.6)	8 (38.1)	6 (27.3)	8 (38.1)	0.449
Hb (g/L), mean ± SD	13.30 ± 1.78	13.00 ± 1.76	12.95 ± 2.1874	12.95 ± 1.7865	0.994
RDW CV, mean ± SD	13.70 ± 1.53	13.65 ± 1.78	14.37 ± 2.08	13.63 ± 1.83	0.252
NLR	2.6 ± 1.24	2.62 ± 1.36	2.90 [1.99–4.12]	2.48 [1.64–3.68]	0.500
PLR	115.0 [77.99–151.28]	97.9 [80.58–169.76]	133.2 ± 56.72	131.2 ± 48.40	0.908
ASA (%)					
II	12 (17.6)	2 (9.5)	3 (13.6)	2 (9.5)	0.179
III	52 (76.5)	16 (76.2)	19 (86.4)	16 (76.2)	
IV	4 (5.9)	3 (14.3)	0 (0)	3 (14.3)	

ACEI, Angiotensin-converting enzyme inhibitor; ASA, American Society of Anesthesiologists Physical Status Classification System; BMI, Body mass index; CAD, Coronary artery disease; CCB, Calcium channel blocker; CHF, Cardiac heart failure; CKD, Chronic kidney disease (creatinine = 132.6 μmol/L/1.5 mg/dl); COPD, Chronic obstructive pulmonary disease; CV, Cardiovascular; Hb, Haemoglobin; IQR, Interquartile range; NLR, Neutrophil Lymphocyte Ratio (pre-psm mean ± SD, post-psm median [IQR 25–75]); PAD, Peripheral artery disease; PLR, Platelet Lymphocyte Ratio (pre-psm median [IQR 25–75, post-psm mean ± SD]; PSM, Propensity Score Match; RDW-CV, red cell distribution width - coefficient of variation; SD, Standard Deviation; TIA, Transient ischemic attack.

Table 2 – Shunt-related surgical techniques and outcomes.

	Before PSM			After PSM		
	Non-Shunt n = 74	Shunt n = 23	P-value	Non-shunt n = 22	Shunt n = 22	P-value
Intended surgical technique, n (%)						
Direct suture	38 (50.7)	0		12 (54.5)	0	
Eversion	16 (21.3)	0		3 (13.6)	0	
Patch	21 (28.0)	22 (95.7)		7 (31.8)	22 (100)	
Surgery time (min), mean ± SD	126.4 ± 36.66	116.6 ± 30.35	0.312	107.3 ± 31.71	113.4 ± 33.51	0.608
Clamping time (min), mean ± SD	43.8 ± 19.98	45.4 ± 22.42	0.784	44.5 ± 24.91	44.4 ± 23.51	0.995

PSM, Propensity Score Match; SD, Standard Deviation.

around 85% of the cases and therefore avoiding likely complications, such as arterial dissection, air/thrombus emboli, and acute occlusion.[6,30–32] A Cochrane meta-analysis by Chongruksut et al. involving 1270 patients from six trials found a trend towards fewer strokes at 30 days with routine shunting vs. no shunting (OR 0.77, 95% CI 0.35–1.69), but no significant differences in mortality were observed. Besides, no significant differences were reported between selective shunting based on stump pressure measurement compared to no shunting.[33] Therefore, due to inconclusive results, current guidelines recommend that the choice of shunting should be left to the decision of the operating surgeon.[12]

Additionally, no association was found between shunting and restenosis. The current evidence on this matter is still scarce. A common hypothesis is that the insertion of a shunt or the use of arterial clamps during shunt insertion could cause early myo-intimal hyperplasia.[34] Cheng et al. also evaluated the long-term restenosis rate in a subset of 790 CEA patients. In this study, 40% of patients were submitted to shunting, but the positive effect on the incidence of restenosis was

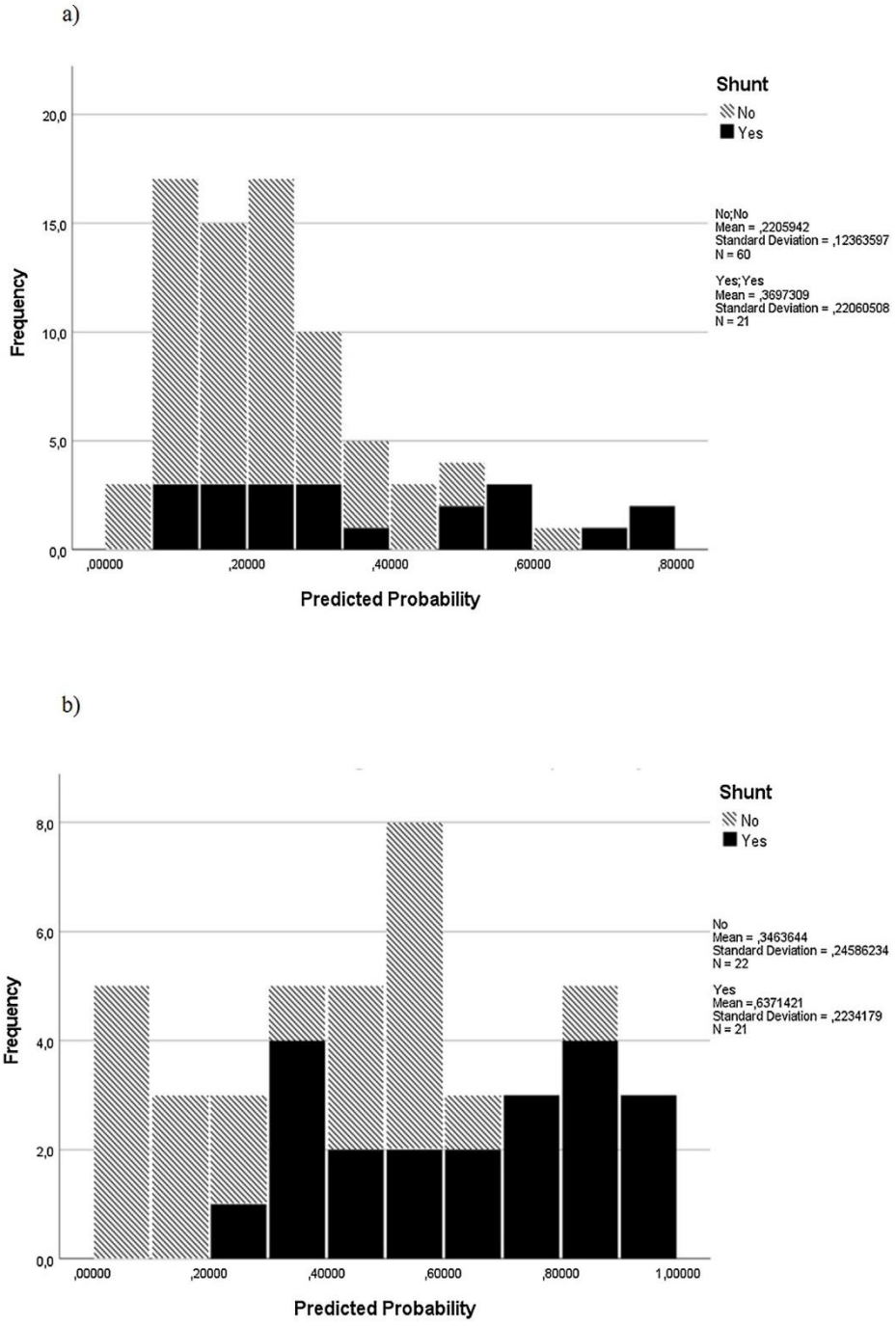

Fig. 1 – Predicted probability distribution (a) pre-propensity score match (b) after propensity score matching.

not confirmed (aHR: 0.83 95% CI 0.61–1.14, P = 0.25 and aHR: 0.96 95% CI 0.52–1.74, P = 0.88 for 50 and 70% stenosis grade, respectively).[34]

The present study holds several limitations aside from being an observational cohort and lacking randomization. This cohort belongs to a large academic teaching institution performing a large proportion of CEA, which might compromise external validity to community hospitals with lower surgical volumes. The guideline and the center patient selection criteria for CEA did not change significantly during the study recruitment and follow-up, although some bias could not be excluded. The specific sample recruited for this study is small in size and has a higher-than-usual event rate resulting from a selection of consecutive positive awake test patients, demanding a cautious interpretation of the results. After propensity score matching, a smaller sample was attained and a lower number of patients with perioperative strokes were acknowledged, with an inherent limited statistical power. Furthermore, the recruitment had a long time frame, due to the low rate of patients with post-CACC neurologic deficits

Table 3 – All patients and subgroup analysis of perioperative adverse events.

Strategy followed	Before PSM				After PSM			
	30 Day-stroke n = 15	P-value	Clavien–Dindo ≥2 n = 25	P-value	30 Day-stroke n = 5	P-value	Clavien–Dindo ≥2 n = 10	P-value
Direct suture (%)	9 (60.0)	0.016	12 (48.0)	0.008	2 (40.0)	0.630	3 (30.0)	0.467
Eversion (%)	3 (20.0)		7 (28.0)		0 (0)		1 (10.0)	
Patch without shunt (%)	0 (0)		0 (0)		0 (0)		0 (0)	
Patch with shunt (%)	2 (13.3)		5 (20.0)		3 (60.0)		6 (60.0)	
Non-shunt (%)	12 (80.0)	0.730	19 (76.0)	0.942	2 (40.0)	0.635	4 (40.0)	0.472
Shunt (%)	3 (20.0)		6 (24.0)		3 (60.0)		6 (60.0)	
Regional anesthesia (%)	13 (86.7)	0.779	22 (88.0)	0.887	5 (100)	0.453	9 (90.0)	0.909
Conversion to GA (%)	2 (13.3)		3 (12.0)		0 (0)		1 (10.0)	

GA, General anesthesia; PSM, Propensity Score Match (shunt and non-shunt).

(8%), during which guidelines and techniques might have improved in between.[35] The option to shunt after the diagnosis of clamping associated with ND was left to the discretion of the surgeon, which might have exposed this study to selection bias.[4]

Further studies with larger samples are still needed to clarify whether perioperative and long-term benefits are superior to the inherent risks of shunting during CEA under RA. However, RCTs are not easy to operationalize due to the low incidence rate of positive awake tests and establish a definitive comparison between a non-shunt and a selective shunt routine.

Conclusions

Incidence of perioperative stroke or further complications (Clavien–Dindo ≥ 2) did not demonstrate significant reduction rates when shunting was applied during CACC in patients submitted to CEA under RA, with a positive awake test. However, more extensive studies and synthesis studies are necessary to clarify the real benefit of shunting regarding short- and long-term outcomes in this subset of patients.

Conflict of interest

None.

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CHAPTER IV

INCIDENCE OF MYOCARDIAL INJURY AFTER NON-CARDIAC SURGERY IN PATIENTS SUBMITTED TO CEA WITH OR WITHOUT REGIONAL ANESTHESIA

CHAPTER IV

Incidence of MINS in patients submitted to CEA with or without RA

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(Part of the results data was used in a Master's Degree in Medicine dissertation)

Review

Incidence of myocardial injury in patients submitted to carotid endarterectomy

A systematic review

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Summary: Myocardial injury following noncardiac surgery (MINS) is associated with higher mortality and major adverse cardiovascular event rates in the short- and long-term in patients undergoing carotid endarterectomy (CEA). However, its incidence is still unclear in this subset of patients. Therefore, this systematic review with meta-analysis aims to determine the incidence of MINS in patients undergoing CEA. Three electronic databases MEDLINE, Scopus, and Web of Science were used to search for studies assessing the occurrence of MINS in the postoperative setting of patients undergoing CEA. The incidence of MINS was pooled by random-effects meta-analysis, with sources of heterogeneity being explored by meta-regression and subgroup analysis (general anesthesia vs. regional anesthesia). Assessment of studies' quality was performed using National Heart, Lung, and Blood Institute Study Quality Assessment Tool, and Risk of Bias 2 tools. Twenty studies were included, with a total of 117,933 participants. Four of them were RCTs, while the remaining were cohort studies. All observational cohorts had an overall high risk of bias, except for Pereira Macedo et al. Three of them had repeated population, thus only data from the most recent one was considered. On the other hand, all RCT had an overall low risk of bias. In patients under regional anesthesia, the incidence of MINS in primary studies ranged between 2% and 15.3%, compared to 0–42.5% for general anesthesia. The meta-analytical incidence of MINS after CEA was of 6.3% [95% CI 2.0–10.6%], but severe heterogeneity was observed (I^2=99.1%). MINS appears to be relatively common among patients undergoing CEA. The observed severe heterogeneity points to the need for further larger studies adopting consistent definitions of MINS and equivalent cut-off values.

Keywords: Myocardial damage, postoperative troponin elevation, carotid revascularization, postoperative cardiovascular events

Introduction

Some patients submitted to noncardiac surgery may experience troponin elevation in the first thirty postoperative days, resulting from myocardial injury [1]. Myocardial injury following noncardiac surgery (MINS) resembles a type two myocardial infarction (MI). It is defined by troponin rising and/or falling patterns, without referred symptoms and/or electrocardiographic findings [2]. Established perioperative non-ischemic diagnosis, such as pulmonary embolism, sepsis, and cardioversion, does not fulfil the criteria for MINS [1]. Selective troponin assessment in patients with a cardiovascular risk superior to 5% evaluated by Revised Cardiac Risk Index, is recommended [3, 4]. The high-sensitivity cardiac troponin, troponins I and T are the current best biomarkers in accessing myocardial injury through troponin assays [2, 5, 6].

The occurrence of MINS withstands a substantial damaging impact on the prognosis of the patient. A prospective cohort study has previously described a 17-fold increased risk of non-fatal MI in vascular patients [7]. Additionally, these patients have shown a 10-fold increased risk of mortality at 30-days after surgery.

Available literature reporting incidence of MINS, which includes vascular surgeries amongst heterogenous samples of noncardiac surgical patients, ranges from 8 to 25%

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[7, 8, 9]. One in every five patients undergoing vascular surgery develop MINS [7]. However, the incidence of MINS has not been systematically assessed for each type of vascular surgery, such is the case for carotid endarterectomy (CEA), which is considered the gold-standard treatment for carotid-stenosis. This has been so even though in short and long-term follow-up, adverse events such as major adverse cardiovascular events (MACE), MI, or acute heart failure also appear to be more common in patients submitted to CEA, who have experienced troponin elevation than those who had not [10, 11, 12].

Therefore, the present systematic aims to determine the incidence of MINS in patients undergoing CEA with or without regional anesthesia (RA), while also exploring the outcomes of populations with and without MINS, and utilizing observational studies, cohort studies, and cross-sectional studies as the chosen study designs.

Materials and methods

This systematic review was conducted in accordance with the Preferred Reporting Items for a Systematic Review and Meta-analysis (PRISMA) Statement and Assessing the methodological quality of systematic reviews (AMSTAR) [13, 14]. An institutional review board's ethical approval was not obtained due to the nature of this study. The review protocol has been registered at Prospero (reference: CRD42021224429).

Selection criteria

Inclusion criteria consisted in all original cohort or experimental studies performed in humans (except for systematic reviews and case series under 20 patients), in which the incidence of MINS after CEA was assessed. Exclusion criteria comprised patients undergoing synchronous cardiac surgery, carotid stenting, or carotid reintervention. No exclusion criteria based on the publication language or date were applied.

Search strategy

A systematic search was performed in three databases – Pubmed, Scopus, and Web of Science –, in February 2023. The query and keywords are shown in Table I. Additionally, the references of the included primary studies and relevant available systematic reviews were screened to search for any further articles of possible interest.

Study selection and data extraction

After duplicates removal, two authors (JPM and AFS) have independently participated in studies selection; any disagreement was solved by the intervention of a third author (JRN). First, studies were selected by title and abstract, and the remaining ones were eligible for full-text assessment. The same samples studied in multiple original articles were only included once. Efforts were made to contact the authors to obtain the full texts that were not publicly available.

Data from included studies were independently extracted by two authors (AFS, JPM). Data were extracted using a purposely built form on the year of publication, country, and centre of recruitment, study design, recruitment time, number of participants undergoing CEA, participants' age, and gender distribution, frequency of cardiovascular comorbidities, and carotid symptomatic status. In addition, data related to each study's MINS cut-off and troponin kit used was retrieved, as well as the incidence and definition of MINS.

Assessment of study quality

Concerning qualitative assessment, the Cochrane Risk of Bias-2 tool was used for randomized clinical trials [15] and the National Heart, Lung, and Blood Institute (NHLBI) Study Quality Assessment Tool was used for observational cohort and cross-sectional studies (2013) [16]. This assessment was independently performed by two authors (JPM and AFS), and when disagreements were observed, decisions were made by mutual consensus after a third-party review (JRN).

Quantitative synthesis

A random-effects meta-analysis (using the restricted maximum likelihood method) of log-transformed proportions to calculate the meta-analytical pooled incidence of MINS among participants was performed. Pooled estimates and 95% confidence intervals (95%CI) were back-transformed into their original scale to simplify their interpretation. Heterogeneity was assessed using the Q-Cochran p-value and the I^2 statistic – a p-value <0.10 and an $I^2 \geq 50\%$ were considered to represent substantial heterogeneity. Sources of heterogeneity were assessed by leave-one-out sensitivity analysis and univariable meta-regression models. Assessed covariates included the publication year, participants' mean age, percentage of male participants, percentage of patients with arterial hypertension, dyslipidemia, diabetes, or coronary artery disease (CAD), percentage of symptomatic patients, percentage of patients using antiplatelet drugs, troponin T levels, troponin I levels, and CK-MB. Subgroup analyses were also performed with separate analyses of studies in which participants were under general anesthesia or regional anesthesia. The possibility of publication biases was assessed using funnel plots.

All statistical analysis were performed using software R (metafor package).

Results

Search results

After the database search and duplicate exclusion, a total of 182 studies were screened. Upon selection by title and

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Table I. Search query – key words

Database	Fields	Search Terms
Pubmed	MeSH Terms	Endarterectomy Endarterectomy, Carotid
		Carotid endarterectomies
		Troponin
	Free text words	Carotid endarterectomy (All fields) Troponin* (All fields)
		Myocardial Injury (All fields)
		cTnT (All fields)
		cTnI (All fields)
	Limits	None
Scopus and Web of Science	Free text words	Endarterectomy Carotid endarterectomy (All fields)
		Carotid endarterectomies (All fields)
		Troponin* (All fields)
		Myocardial Injury (All fields)
		cTnT (All fields)
		cTnI (All fields)
	Limits	None

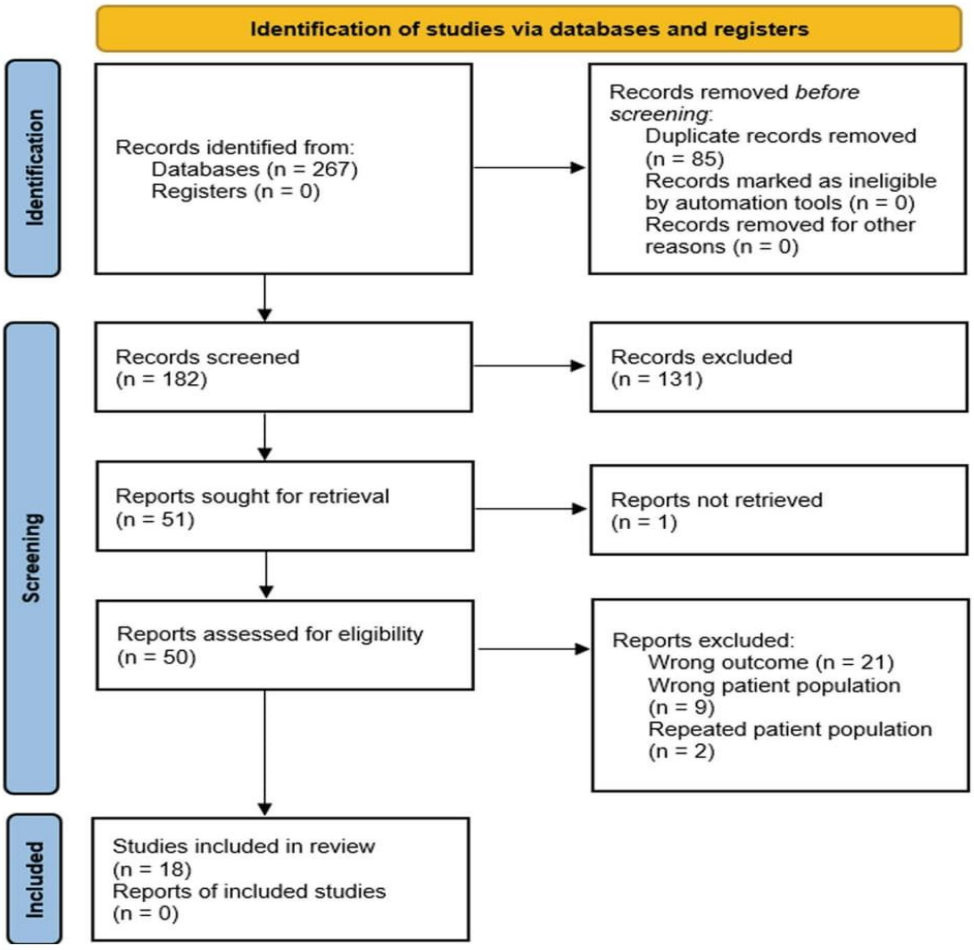

Figure 1. Flow-diagram according to PRISMA statement regarding the process of identification and selection of the studies.

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Table II. Identification and summary description of the selected studies from where data were retrieved

Author	Journal	Publication year	Study design	Study center	Recruitment time	Sample size (patients)	No. CEA
Aridi et al. [17]	Journal of Vascular Surgery	2017	Retrospective from prospective database	Baltimore, USA multicenter, Johns Hopkins Bayview Vascular and Endovascular Research Center, USA	January 2003–February 2017 (14 years)	75319	75319
Cnotliwy et al. [18]	Acta Angiologica	2011	Prospective observational study	Pomeranian Medical University, Szczecin, Poland	NA	100	100
Feng et al. [19]	Clinical and Applied Thrombosis/Hemostasis	2013	Prospective observational study	XuanWu Hospital of Capital Medical University, China	May 2010–March 2012 (22 months)	40	40
Feringa et al. [20]	Coronary artery disease	2007	Retrospective from prospective database	Erasmus Medical Center in Rotterdam	2005–2006 (1 year)	44	44
Galyfos et al. [11]	Journal of Stroke and Cerebrovascular Diseases	2015	Prospective observational study	University of Athens Medical School, Hippocration Hospital, Athens	January 2003–June 2013 (126 months)	324	324
Garcia et al. [21]	Journal of the American Heart Association	2016	RCT	Minneapolis Veterans Affairs Healthcare System, USA	June 2011–September 2015 (51 months)	49	49
Grobben et al. [12]	European Journal of Vascular and Endovascular Surgery	2015	Prospective observational study	University Medical Center Utrecht, The Netherlands	January 2011–December 2013 (3 years)	225	225
Hye et al. [22]	Journal of Vascular Surgery	2016	Prospective, randomized, multicenter trial with blinded end point adjudication	NA: 117 clinical centers in the United States and Canada	December 2000–July 2008	1149	1149
Jellish et al. [23]	Journal of neurosurgical anesthesiology	2003	RCT	Loyola University Medical Center, Maywood, Illinois, USA	NA	59	59
Pereira-Macedo et al. [10]	International Journal of Surgery	2019	Prospective cohort	Portuguese tertiary care	January 2009–January 2018 (9 years)	156	156
Kwon et al. [24]	Journal of Neurosurgery	2016	Retrospective study of data from a prospective CEA registry	Asan Medical Center	January 2005–December 2014 (10 years)	666	666
Leblanc et al. [25]	Anesthesia Critical Care & Pain Medicine	2015	Prospective observational study	Institut Mutualiste Montsouris, French	April 2011–May 2013 (25 months)	50	50
Motamed et al. [26]	Journal of Vascular Surgery	2005	Prospective observational study	Single university Hospital, French	July 1998–December 1999 (17 months)	75	75
Shukla et al. [27]	Annals of Vascular Surgery	2019	Prospective observational study	Rural academic medical centre of University of Vermont Medical Center	January 2016–December 2016 (12 months)	78	78
Steely et al. [28]	Annals of Vascular Surgery	2017	Retrospective from prospective database	Multicenter VQI	January 2010–December 2014 (4 years)	39118	39118
Tyson et al. [29]	Annals of Vascular Surgery	2019	Retrospective from prospective database	Single center, NY	February 2011–July 2015 (54 months)	289	289
Walsh et al. [30]	Vascular and Endovascular Surgery	2010	RCT	Cambridge Vascular Unit	January 2006–May 2008 (29 months)	70	70
Wang et al. [31]	Chinese Medical Journal	2015	RCT	Single center of Beijing, Xuan Wu Hospital, Capital Medical University	November 2011–December 2013 (25 months)	122	122

Notes. CEA: carotid endarterectomy; RA: regional anesthesia.

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Table III. Demographics and comorbidities of the population samples for each study

Author	Mean age	Male n (%)	Arterial hypertension n (%)	Dislipidemia n (%)	Diabetes mellitus n (%)	Smoking history n (%)	Coronary artery disease n (%)	Carotid territory symptoms n (%)
Aridi et al. [17]	71.1	45498 (60.4)	66 821 (88.7)	60275 (80.0)	26325 (35.0)	57007 (75.7)	20710 (27.5)	23091 (30.7)
Cnotliwy et al. [18]	69.4	66 (66.0)	85 (85.0)	NA	35 (35.0)	NA	47 (47.0)	61 (61.0)
Feng et al. [19]	67.0	32 (80.0)	31 (77.5)	27 (67.5)	14 (35.0)	25 (62.5)	6 (15.0)	40 (100)
Feringa et al. [20]	64.0	34 (77.3)	18 (40.9)	29 (65.9)	6 (13.6)	29 (65.9)	13 (29.5)	NA
Galyfos et al. [11]	67.3	207 (64.0)	289 (89.0)	168 (52.0)	93 (29.0)	171 (53.0)	NA	143 (44.0)
Garcia et al. [21]	NA	49 (100)	NA	NA	NA	NA	NA	NA
Grobben et al. [12]	73.0	164 (73.0)	188 (83.6)	182 (81.0)	57 (25.3)	67 (29.8)	NA	202 (89.7)
Hye et al. [22]	69.1	769 (67.0)	989 (86.1)	986 (85.8)	355 (30.9)	299 (26.0)	588 (51.1)	611 (53.2)
Jellish et al. [23]	70.7	34 (58.0)	NA	NA	NA	NA	NA	NA
Pereira-Macedo et al. [10]	69.6	119 (76.3)	133 (85.3)	127 (81.4)	62 (39.7)	79 (50.6)	57 (36.5)	62 (39.7)
Kwon et al. [24]	68.7	573 (86.0)	498 (74.8)	NA	239 (35.9)	424 (63.7)	45 (6.8)	364 (54.7)
Leblanc et al. [25]	72.0	37 (74.0)	NA	NA	NA	NA	14 (28.0)	10 (20.0)
Motamed et al. [26]	72.0	63 (84.0)	58 (77.3)	NA	14 (18.7)	40 (53.3)	NA	42 (56.0)
Shukla et al. [27]	NA	53 (68.0)	67 (86.0)	78 (100)	26 (33.3)	63 (80.7)	20 (25.6)	47 (60.3)
Steely et al. [28]	NA	NA	NA	NA	NA	NA	NA	NA
Tyson et al. [29]	70.2	172 (59.5)	267 (92.4)	232 (80.6)	NA	225 (78.0)	NA	NA
Walsh et al. [30]	68.9	49 (70.0)	44 (62.9)	62 (88.6)	15 (21.4)	38 (54.3)	23 (32.8)	42 (60.0)
Wang et al. [31]	66.2	110 (90.2)	82 (67.2)	20 (16.4)	32 (26.2)	61 (50.0)	22 (18.0)	122 (100)

Notes. NA: unavailable data.

abstract, 131 studies were excluded. Fifty-one studies were eligible for full-text assessment, and, during this process, 31 studies were excluded, and one was not retrieved (Figure 1). Comprehensive reasons for exclusion upon full-text assessment were: patients undergoing synchronous cardiac surgery, carotid stenting, or carotid reintervention (N=9), absence of assessment of MINS (N=21), and absence of full-text even after contacting the respective author (N=1). Thus, a total of 20 published articles were included in this systematic review [10, 11, 12, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31] (Table II).

Description of studies

Sixteen of the 20 studies included in this systematic review were observational cohorts, five of them being retrospective [17, 20, 24, 28, 29]. However, two studies had repeated samples that were next included in a more recent article, and therefore only data from the latter was considered [11, 32, 33]. The other four studies were randomized controlled trials (RCT) [21, 23, 30, 31]. The included publications were performed in 10 different countries within 3 continents – six from North America [17, 21, 22, 23, 27, 29], nine from European countries [10, 11, 12, 18, 20, 25, 26, 28, 30], and three studies from Asia [19, 24, 31]. A total of 117,933 patients were assessed, with a minimum of 40 [19] and a maximum of 75,319 [17] patients per study. The mean participants' age was 69.2 years old. The percentage of male participants was 40.7% (n=48,029). Demographics and comorbidities of the populations included in the studies were gathered and are available in Table III. Data related to periprocedural setting, such as type of anesthesia and previous use of antiplatelet/anticoagulation therapy, is displayed in Table IV.

MINS was defined according to the Fourth Universal Definition of Myocardial Infarction in six of the studies [2, 10, 18, 19, 22, 28, 31], while Grobben et al. and Garcia et al. [12, 21] followed the Third Universal Definition, which is similar to the former one. The Vascular Quality Initiative database used in one of the included studies defined MINS according to their criteria, which, likewise, are comparable to the Fourth Universal Definition [17]. Tyson et al. [29] determined the diagnosis of MI as a troponin I value equal or above to 0.6 ng/mL or CK-MB is >6.3 ng/mL together with correlation with electrocardiographic changes. Galyfos et al. [11] and Kwon et al. [24] followed the British Cardiac Society international guidelines of MI definition [24, 34], while Motamed et al. [26] conformed to the definition of the Joint European Society of Cardiology/American College of Cardiology guidelines [35]. Feringa et al used the lower reference limit of detection (>0.03 ng/ml) of the kit to define troponin elevation only [20]. Hye et al. [22] used troponin I, T, and CK-MB for the assessment of MINS, while Tyson et al. [29] recurred to troponin I and CK-MB markers. Troponin I and hSTnI were both used by Pereira-Macedo et al. [10]. Troponin I alone was used in thirteen articles [11, 12, 17, 18, 19, 21, 23, 24, 25, 26, 27, 30, 31] and only one article [20] used troponin T alone. Two articles did not specify which biomarkers were used [17, 28]. Additionally, Jellish et al., Leblanc et al., Walsh et al., and Shukla et al. [23, 25, 27, 30] did not state any MINS definitions. Troponin measurement kits were retrieved as displayed in Table V.

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Table IV. Relevant data related to the surgical setting: presence of contralateral disease, antiplatelet and anticoagulation therapies and type of anesthesia

Author	Contralateral stenosis n (%)	Antiplatelet therapy n (%)	Dual antiplatet therapy n (%)	Anticoagulation n (%)	General anestesia n (%)	Regional anestesia n (%)
Aridi et al. [17]	NA	62519 (83.0)	NA	5687 (75.5)	68635 (91.1)	6684 (8.9)
Cnotliwy et al. [18]	NA	NA	NA	NA	12 (12.0)*	100 (100)*
Feng et al. [19]	9 (22.5)	19 (47.5)	NA	NA	40 (100)	0 (0.0)
Feringa et al. [20]	NA	41 (93.2)	NA	NA	NA**	NA**
Galyfos et al. [11]	NA	324 (100)	NA	NA	324 (100)	0 (0.0)
Garcia et al. [21]	NA	NA	NA	NA	49 (100)	0 (0.0)
Grobben et al. [12]	50 (22.2)	196 (87.1)	NA	NA	225 (100)	0 (0.0)
Hye et al. [22]	NA	NA	NA	NA	1038 (90.3)	111 (9.7)
Jellish et al. [23]	NA	NA	NA	NA	59 (100)	0 (0.0)
Pereira-Macedo et al. [10]	NA	156 (100)	0 (0.0)	156 (100)	0 (0.0)	156 (100)
Kwon et al. [24]	NA	363 (54.5)	NA	NA	375 (56.3)	0 (0.0)
Leblanc et al. [25]	NA	50 (100)	4 (8.0)	6 (12.0)	0 (0.0)	50 (100)
Motamed et al. [26]	NA	52 (69.0)	NA	NA	39 (52.0)	NA
Shukla et al. [27]	NA	78 (100)	20 (25.6)	5 (6.4)	77 (99.0)	NA
Steely et al. [28]	NA	NA	NA	NA	NA	NA
Tyson et al. [29]	NA	250 (86.5)	NA	NA	289 (100)	0 (0.0)
Walsh et al. [30]	NA	63 (90.0)	18 (25.7)	NA	70 (100)	0 (0.0)
Wang et al. [31]	NA	NA	NA	NA	122 (100)	0 (0.0)

Notes. NA: unavailable data. * – 12 conversions of RA to GA during intervention; ** – combination of GA and RA.

Main findings and meta-analysis

The incidence of reported MINS within 30-days after CEA in primary studies ranged from 0 and 42.5%. Considering only patients submitted to RA, a range of 2–15.3% was observed in the occurrence of MINS, while among patients submitted to GA such range was of 0–42.5%.

Concerning short- and long-term outcomes in patients that experienced MINS, available data was sparse but further withdrawn and displayed in the Tables VI and VII.

The meta-analytical incidence of MINS after CEA was 5.5% [95% CI 2.8–12.0%]. However, severe heterogeneity was found (I^2=99.1%; Q-Cochran p-value<0.001). Notably, it is worth mentioning that only two studies exhibited MINS incidences exceeding 20%. In all results of leave-one-out sensitivity analysis and of univariable meta-regression models, severe heterogeneity was described (I^2>90%) (Tables VIII and IX). Additionally, subgroup analysis regarding the use of general anesthesia vs. regional anesthesia has shown similar high heterogeneity (above 98 and 96%, respectively). Studies related to general anesthesia have reached a prevalence of 4.5% whereas regional anesthesia accounted with 2.2% of MINS, in the meta-analysis (Table VIII).

Studies quality

The risk of bias of the selected articles is displayed in Figures 2, 3, 4 and 5. The risk of bias for each observational cohort is individually displayed in Figure 2, while the risk of bias for each RCT is displayed in Figure 3. The overall judgement per evaluated item regarding observational cohorts is shown in Figure 4, whereas the one regarding RCT is shown in Figure 5.

All observational cohorts had an overall high risk of bias, except for Pereira Macedo et al. [10]. On the other hand, all RCT had an overall low risk of bias [21, 23, 30, 31]. The items most frequently associated with high risk of bias amongst observational cohorts included sample size justification, power description, variance and effect estimates, exposure assessment, key potential confounding variables measurement, and statistical adjustment for their impact.

Publication bias

A funnel plot regarding publication bias is displayed in Figure 6. The funnel plot displays an asymmetric pattern – while funnel plot asymmetry is expected in cases of severe heterogeneity, publication bias cannot be excluded.

Discussion

The present systematic review has found a meta-analytical incidence of MINS after CEA of 5.5%, with a range between 0% and 42.5%. However, severe heterogeneity was found and not accounted by sensitivity analysis or meta-regression models.

MINS has been the subject of increasing interest to clinical researchers. In fact, despite being an asymptomatic troponin elevation finding that occurs within 30-days after

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Table V. MINS definitions, troponin cut-off values and troponin kits used in the centers

Author	MINS n (%)	MINS definition	Troponin T vs I	Troponin kit	Kit troponin limit
Aridi et al. [17]	285 (3.8)	Troponin rise alone was reported if there was a rise in cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and in the absence of the six qualifying criteria for MI or sudden death as defined by the VQI.	NA	NA	One value above the 99th percentile upper reference limit
Cnotliwy et al. [18]	12 (12.0)	Only this: Myocardial infarction and sudden cardiac death defined according to the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction.	Trop I	VIDAS Troponin I Ultra immunoassay and VIDAS BLUE analyzer, bioMerieux INC., Durham	NA
Feng et al. [19]	17 (42.5)	Myocardial injury is indicated if the cTnI concentration is above 0.04 ng/mL.	Trop I	AxSYM Troponin-I ADV assay (Abbott Laboratories) on a routine AxSYM analyzer	Myocardial injury >0.04 ng/mL; Myocardial ischemia 0.05–1.5 ng/mL; Myocardial infarction >1.5 ng/mL
Feringa et al. [20]	2 (4.5)	Troponin T levels were measured on postoperative days 1, 3, 7 or before discharge and whenever clinically indicated by ECG changes, consistent with myocardial ischemia or infarction.	Trop T	Electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics, Mannheim, Germany)	Lower limit positive detection >0.03 ng/ml
Galyfos et al. [11]	8 (2.4)	Postoperative cTnI values ranging from .05 ng/mL to .5 ng/mL were classified as MIsch and cTnI values over 0.5 ng/mL as MIn, even in the absence of symptoms, according to international guidelines. The occurrence of MIsch or MIn was defined as cardiac damage.	Trop I	Architect; Abbott Corporation Ltd, North Chicago, IL	cTnI normal value cutoff was .05 ng/mL
Garcia et al. [21]	10 (21.0)	Proportion of subjects with a detectable increase in cardiac troponin I (cTnI) within 72 hours of vascular surgery and the distribution of such increases. A detectable increase was defined as having 1 postoperative cTnI measurement above the preoperative cTnI with at least 1 of the postoperative values above the 99th percentile for the assay. We also evaluated the proportion of patients meeting the Third Universal Definition of MI. According to this definition a MI is present when there is evidence of myocardial necrosis (ie, rise and fall of cardiac biomarker) and one of the following (s): symptoms of myocardial ischemia, developing of pathological Q waves or new ischemic changes (1-mm horizontal or downsloping STdepression, new 2-mm-deep T-wave inversion, ≥1 mm STsegment elevation in 2 contiguous leads, or new left bundle branch block) in the electrocardiogram (ECG), imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, and/or identification of an intracoronary thrombus by angiography or autopsy.	Trop I	Abbott ARCHITECT cTnI assay; Siemens Dimension Vista cTnI assay	>0.028 lg/L; >0.021 lg/L, respectively
Grobben et al. [12]	26 (11.0)	Patients were classified as troponin only in case of troponin elevation without angina or ischemic changes on the ECG (based on the most recent definition of MI – 3rd universal definition).	Trop I	Third generation AccuTnI assay (Beckman Coulter, Brea, CA)	Upper reference limit of 60 ng/L;
Hye et al. [22]	12 (10.4)	Cardiac ischemia was biomarker elevation alone were included in the analysis and were labeled as biomarker-only MI.	Trop T, I and CK-MB	NA	CK myocardial band (CK-MB) or troponin levels were two or more times the upper limit of the local site laboratory's normal value.
Jellish et al. [23]	0 (0.0)	NA	Trop I	NA	Increment compared with preoperative values

(Continued on next page)

Table V. (Continued)

Author	MINS n (%)	MINS definition	Troponin T vs I	Troponin kit	Kit troponin limit
Pereira-Macedo et al. [10]	24 (15.3)	Myocardial injury after noncardiac surgery (MINS) is defined as a relevant myocardial injury due to ischemia occurring during or within 30 days after surgery. Myocardial injury after noncardiac surgery is defined by a rising pattern of cardiac troponin values with at least one value above the 99th percentile upper reference limit.	Trop I; hSTnI	Trop I chemiluminescent microparticle immunoassay (Architect Stat Troponin I, Abbot Laboratories, Wiesbaden, Germany) and a fourth-generation assay hSTnI (Abbot Laboratories, Wiesbaden, Germany)	Trop I: 0.032 μg/mL regardless of sex; hsTnI27 ng/mL (male) or 11.4 ng/mL (female)
Kwon et al. [24]	6 (1.0)	Cardiac damage was defined as postoperative elevation of the blood concentration of cardiac troponin I (0.05–0.5 ng/ml) in the absence of myocardial ischemia.	Trop I	NA	0.05–0.5 ng/ml
Leblanc et al. [25]	1 (2.0)	CTnI up to 0.95 ng.ml−1 (day 2) without ECG changes.	Trop I	NA	cTnI up to 0.95 ng.ml−1
Motamed et al. [26]	10 (13.3)	CTnI values of between 0.5 and 1.5 ng/mL were considered myocardial ischemia.	Trop I	Stratus analyzer (Dade, Massy, France). At the time of the study, the detection limit of the immunoassay was 0.1 ng/mL.	0.5 and 1.5 ng/mL
Shukla et al. [27]	5 (6.4)	NA	Trop I	Immunoassay testing via monoclonal antibody binding with >0.034 ng/mL defined as abnormal (Ortho Clinical Diagnostics, Raritan, New Jersey).	>0.034 ng/mL
Steely et al. [28]	15647 (0.4)	Troponin-only POMI was defined as troponin elevation beyond the normal upper limit without creatinine phosphokinase muscle brain elevation and without other clinical signs, symptoms, or ECG changes consistent with myocardial infarction (MI).	NA	NA	NA
Tyson et al. [29]	5 (1.7)	A patient was judged to have an Myocardial infarction if the troponin-I level was greater than or equal to 0.6 ng/mL or CK-MB is >6.3 ng/mL (as per our institutional parameters). This was further qualified by the presence or absence of symptoms and changes on electrocardiography (EKG) or echocardiogram. A patient was judged to have an MI on EKG if the patient developed ST elevation, Q waves, or T wave inversion on postoperative EKG. Furthermore, echocardiogram findings of new wall motion abnormality, decreased ejection fraction, or new left ventricular dysfunction postoperatively indicated acute MI.	Trop I; CK-MB	NA	Trop I >0.6 ng/mL or CK-MB >6.3 ng/mL
Walsh et al. [30]	2 (2.9)	Elevation in serum troponin I >0.15 mg/dL	Trop I	NA	>0.15 mg/dL
Wang et al. [31]	25 (20.5)	The primary end-point was the rate of myocardial injury, as measured by cTnI. In the healthy population, the 99 percentile value of cTnI is 0.04 ng/ml; thus, the myocardial injury was defined as a cTnI > 0.04 ng/ml.	Trop I	AxSYM troponin I analyser (Abbott Laboratories, Longford, Ireland)	Lower limit of detection 0.02 ng/mL. MINS>0.04

Notes. NA: unavailable data.

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noncardiac surgery, several studies have shown that its prognostic effect might be deleterious for the patients at short and long-term periods, which turns this topic into a focus of concern in clinical practice [1, 7, 10, 12]. The diagnostic criteria for MINS diverge from the criteria for MI, and its occurrence may be pathophysiologically explained by oxygen supply or demand imbalance in the postoperative period [2]. For vascular surgery, it is known that the surgical procedure itself is considerably associated with a higher risk of cardiovascular events [36]. Additionally, a previous meta-analysis regarding vascular surgery has found that MINS was a predictor of all-cause postoperative mortality at 30 days [37]. Such systematic review has identified a 15.5% incidence of patients experiencing myocardial lesion after vascular surgery [37].

However, the incidence of MINS after CEA is not widely reported. Likewise, its therapeutic approach and prognostic potential are not well established. Due to its likely impact on prognosis, management of MINS is vital, and it is a major concern of clinical research. In fact, MINS is associated to a 3-fold increased risk of death and a 14-fold risk of myocardial infarction. Concerning patients undergoing CEA, a reported 15% incidence of major cardiovascular events have been reported [1, 7, 12]. Nonetheless, how to manage these patients is still a challenge. A recently published trial, MANAGE trial found a protective effect of the administration of dabigatran 110 mg twice daily on significantly lowering the risk of major vascular adverse events, without significantly increasing the risk of major bleeding [38].

In regard of CEA and the occurrence of postoperative MINS on the present systematic review, only three cohort studies – Cnotliwy et al. [18], Pereira-Macedo et al. [10], and Leblanc et al. [25] have performed CEA under RA while other ten studies, including all the randomized control trials, executed CEA under GA [11, 12, 19, 21, 23, 24, 26, 29, 30, 31]. Two studies did not specify the anesthetic approach [20, 28]. The remaining three studies performed both RA and GA but did not discriminate MINS incidence between the two procedures [17, 22, 27]. The samples of the studies whose patients were submitted to RA are small, ranging from 50 to a maximum of 150 individuals, which compromises the precision of the results. On the other hand, most of the studies were performed under GA, assessing larger samples of patients.

Since RA is reasonable in clinical practice and may be associated with fewer adverse effects, it is expected to have a lower incidence of troponin elevation. Furthermore, GA stands for a more challenging hemodynamic management, which could prompt myocardial blood flow imbalances. However, the GALA trial suggests that no differences in MI occurrence are expected between CEA patients submitted to RA or those submitted to GA, as well as in the postoperative quality of life, length of hospital stay, stroke, or death [39]. Yet, the incidence of MINS has not been widely studied, and the impact of the anesthetic approach is still unclear.

Feng et al. [19] has found an association between MINS and symptomatic carotid stenosis (defined by authors as >70% of the luminal diameter on colour duplex ultrasonography) and ST-segment changes consistent with ischemia, although none of these associations were confirmed by multivariable logistic regression analysis. Moreover, they have detected significant changes in hemodynamic parameters such as higher cardiac output and stroke volume indexes and lower diastolic and mean arterial pressures in patients with abnormal cardiac troponin.

The potential interference of dual antiplatelet therapy (DAPT) with the incidence of MINS is acknowledged. Still, the absence of substantial data prevents the establishment of a direct link, as only four studies in our review reported DAPT usage and available literature within the search scope did not provide evidence of significant differences between DAPT and SAPT in altering MINS incidence (Table IV).

In Grobben et al. [12], the 34 patients that experienced troponin elevation after CEA had a significantly higher prevalence of chronic kidney disease (glomerular filtration rate <45 mL/min), symptomatic presentation, and primary/bovine patch closure than the patients with no troponin elevation. However, only 26 of those 34 patients were diagnosed with MINS, while the remaining patients were diagnosed with perioperative MI. Since the reported baseline characteristics were not discriminated between these two groups of patients with troponin elevation, extrapolation could result in an overestimating effect. Four percent of MINS patients experienced short-term MACE (1 stroke), defined as the composite of MI, stroke, and cardiovascular death, and 8% at 1.8 years follow-up (4% stroke, 4% cardiovascular death, and 12% all-cause mortality).

In Pereira-Macedo et al. [10], chronic heart failure was independently associated with the occurrence of MINS with a 4-fold increased risk in patients submitted to RA, whereas coronary artery disease (CAD) was not confirmed as a statistically significant risk factor. CAD is currently the leading cause of heart failure [40] and plays an important role in postoperative myocardial events in vascular patients [41, 42]. The majority of patients enrolled for vascular surgery had a prior history of CAD. Biccard et al., that studied a large prospective cohort, also did not confirm CAD as a risk factor for incidence of MINS in vascular patients [7]. Therefore, it can be suggested that CAD may present significant interaction and act as a confounding factor.

Only two studies (Pereira-Macedo et al. and Grobben et al.) [10, 12] have assessed the impact of MINS at short and long-term follow-up. Both have found a solid potential role of MINS in the occurrence of cardiovascular events. However, in Grobben et al. [12], results should be carefully scrutinized since only 26 patients of the 34 with troponin elevation had experienced the full criteria of MINS. Nevertheless, Pereira-Macedo et al. [10] have found a significant impact regarding the occurrence of MACE and acute MI at 52 months follow-up.

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Table VI. Short-term outcomes after CEA for patients who developed MINS

Author	Stroke 30 days n (%)	Stroke/Death 30 days n (%)	Death 30 days n (%)	MI 30 days n (%)	MACE 30 days n (%)	MACE definition	Post-operative complications 30 days n (%)
Aridi et al. [17]	NA	NA	NA	NA	NA	NA	NA
Cnotliwy et al. [18]	NA	NA	NA	NA	NA	NA	NA
Feng et al. [19]	NA	NA	NA	0 (0.0)	NA	NA	NA
Feringa et al. [20]	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Galyfos et al. [11]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA
Garcia et al. [21]	NA	NA	0 (0.0)	NA	NA	NA	NA
Grobben et al. [12]	1 (3.8)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	Composite of MI, stroke and cardiovascular death	NA
Hye et al. [22]	NA	NA	0 (0.0)	NA	NA	NA	NA
Jellish et al. [23]	0 (0)	0 (0)	0 (0.0)	0 (0.0)	NA	NA	NA
Pereira-Macedo et al. [10]	1 (4.1)	2 (8.3)	NA	1 (4.1)	1 (4.3)	Composite of MI, acute heart failure and all-cause mortality	NA
Kwon et al. [24]	NA	NA	NA	NA	NA	NA	NA
Leblanc et al. [25]	0 (0.0)	0 (0.0)	NA	0 (0.0)	NA	NA	NA
Motamed et al. [26]	0 (0.0)	NA	NA	NA	NA	NA	NA
Shukla et al. [27]	NA	NA	NA	NA	NA	NA	NA
Steely et al. [28]	NA	NA	NA	NA	NA	NA	NA
Tyson et al. [29]	NA	NA	NA	NA	NA	NA	NA
Walsh et al. [30]	0 (0.0)	NA	NA	0 (0.0)	NA	NA	2 (2.9)
Wang et al. [31]	NA	NA	NA	NA	NA	NA	NA

Notes. NA: unavailable data.

Seven of the papers did not offer information regarding the equipment utilized, and considering their respective definitions of MINS it is challenging to interpret the results. Indeed, when a kit is identified, a cut-off of troponin detection, is established along with the definition of MINS used by the authors. According to the Fourth Universal Definition of MI, MINS is defined by a rising of cardiac troponins with at least one value above the 99th percentile upper reference limit [2]. Centres that did not mention the cut-off limits inferred the diagnosis of MINS according to their institution protocols, which conveys some inconsistency amid the selected studies. Therefore, the derived outcomes should be judiciously revised. When the definition of MINS varied from the current guidelines, interpretation of the results considered this issue to avoid erratic analysis.

This systematic review exposes the need for large cohorts and RCTs that implement standardized methodology and apply consistent definitions of MINS, with a primary aim to assess the incidence and effect of MINS in patients undergoing CEA to validate the current findings in the literature and further uncover the existing gaps of knowledge. Furthermore, observational cohorts should avoid the frequent bias detected in this study, by presenting sample size justification, power description, variance and effect estimates, exposure assessment, key potential confounding variables measurement, and statistical adjustment for their impact.

In truth, the potential impact of MINS might predispose clinicians to adapt their strategies for better management of these patients. Nonetheless, more studies regarding the prevention and management of MINS are crucial to avoid further harm to the patients at short and long periods.

Limitations

This study faced many limitations worth noting. First, few articles were eligible for this systematic review, and the majority of those had a small sample size without sample justifications and power descriptions, which led to low precision of obtained results and consequently might affect external validity. Furthermore, despite having a low risk of bias, the included RCTs aimed to study different primary outcomes other than MINS, even though the authors analysed and assessed MINS prevalence and characterisations. Additionally, it is essential to enhance that RCTs' design infers selection bias, since patients are carefully chosen to meet their criteria. On the other hand, there was severe heterogeneity amongst studies regarding most baseline patient characteristics, study designs, and methodology, prompting a high diversity of MINS definitions and troponin kits used. In fact, differences between primary studies were so extensive that, in meta-regression, any single variable could be identified, which could possibly account for most heterogeneity. The authors were not able to perform multivariable meta-regression models on account of the insufficient number of included primary studies. Few other short- and long-term outcomes were assessed, such as stroke, MI, MACE or death, which deprived the study of MINS association with other outcomes.

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Table VII. Long-term outcomes after CEA in patients who developed MINS

Author	Other outcomes	Long-term outcomes	Long-term follow-up time	Long-term MI n (%)	Long-term stroke n (%)	Long-term MACE n (%)	Long-term all-cause mortality n (%)
Aridi et al. [17]	NA	NA	NA	NA	NA	NA	NA
Cnotliwy et al. [18]	NA	NA	NA	NA	NA	NA	NA
Feng et al. [19]	NA	NA	NA	NA	NA	NA	NA
Feringa et al. [20]	NA	NA	1.2 years	0 (0.0)	NA	NA	NA
Galyfos et al. [11]	NA	NA	2 years ± 2.2 months	NA	NA	NA	NA
Garcia et al. [21]	NA	NA	6 months	NA	NA	NA	NA
Grobben et al. [12]	NA	NA	1.8 years [IQR 1.0–2.6]	0 (0.0)	1 (4.0)	2 (8.0)	3 (12.0)
Hye et al. [22]	NA	NA	NA	NA	NA	NA	NA
Jellish et al. [23]	NA	NA	NA	NA	NA	NA	NA
Pereira-Macedo et al. [10]	NA	MI, stroke, MACE, all-cause mortality	52 months [49–54]	HR: 3.318. 95% CI: 0.97–13.928. Breslow: P=0.025	HR: 2.133. 95% CI: 0.565–8.052 P=0.251	HR: 1.955. 95% CI: 1.01–4.132. Breslow: P=0.046	HR: 1.699 95% CI: 0.772–3.743. log rank: P=0.986)
Kwon et al. [24]	NA	NA	NA	NA	NA	NA	NA
Leblanc et al. [25]	NA	NA	NA	NA	NA	NA	NA
Motamed et al. [26]	NA	NA	44±12 months	NA	NA	NA	NA
Shukla et al. [27]	NA	NA	NA	NA	NA	NA	NA
Steely et al. [28]	NA	NA	NA	NA	NA	NA	NA
Tyson et al. [29]	NA	NA	NA	NA	NA	NA	NA
Walsh et al. [30]	NA	NA	NA	NA	NA	NA	NA
Wang et al. [31]	NA	NA	NA	NA	NA	NA	NA

Notes. NA: unavailable data.

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Table VIII. Meta-analysis results and subgroup analysis

Meta-analysis results	N studies	Proportion	CI_LB	CI_UB	Heterogeneity_I2	Heterogeneity_p-value
All studies	18	0.055	0.028	0.110	99.1	<0.001
General Anesthesia	12	0.045	0.018	0.113	98.1	<0.001
Regional Anesthesia	4	0.022	0.004	0.115	96.4	<0.001

Notes. CI: confidence interval; LB: lower bound; UB: upper bound.

Table IX. Meta-regression results

Meta-regression results	N studies	Odds Ratio	CI_LB	CI_UB	p-value	Heterogeneity_I2	Heterogeneity_p-value
Year	18	0.992	0.844	1.166	0.923	99.1	<0.001
Mean age	15	0.889	0.641	1.233	0.482	97.2	<0.001
Percent of males	17	1.073	1.020	1.129	0.007	94.8	<0.001
Percent of AHT	14	0.980	0.923	1.040	0.503	97.3	<0.001
Percent of dyslipidemia	11	0.979	0.941	1.018	0.283	97.8	<0.001
Percent of diabetes	13	0.984	0.880	1.100	0.774	97.8	<0.001
Percent of smokers	13	0.983	0.935	1.033	0.499	97.1	<0.001
Percent of CAD	11	0.990	0.918	1.067	0.787	98.2	<0.001
Percent of symptomatic	13	1.042	1.015	1.069	0.002	95.1	<0.001
Percent of antiplatelet use	12	0.987	0.941	1.035	0.581	97.3	<0.001
Troponin T	16	0.758	0.046	12.468	0.846	94.8	<0.001
Troponin I	15	1.440	0.374	5.542	0.596	94.5	<0.001
CKMB	16	0.268	0.022	3.310	0.304	94.3	<0.001

Notes. CI: confidence interval; LB: lower bound; UB: upper bound.

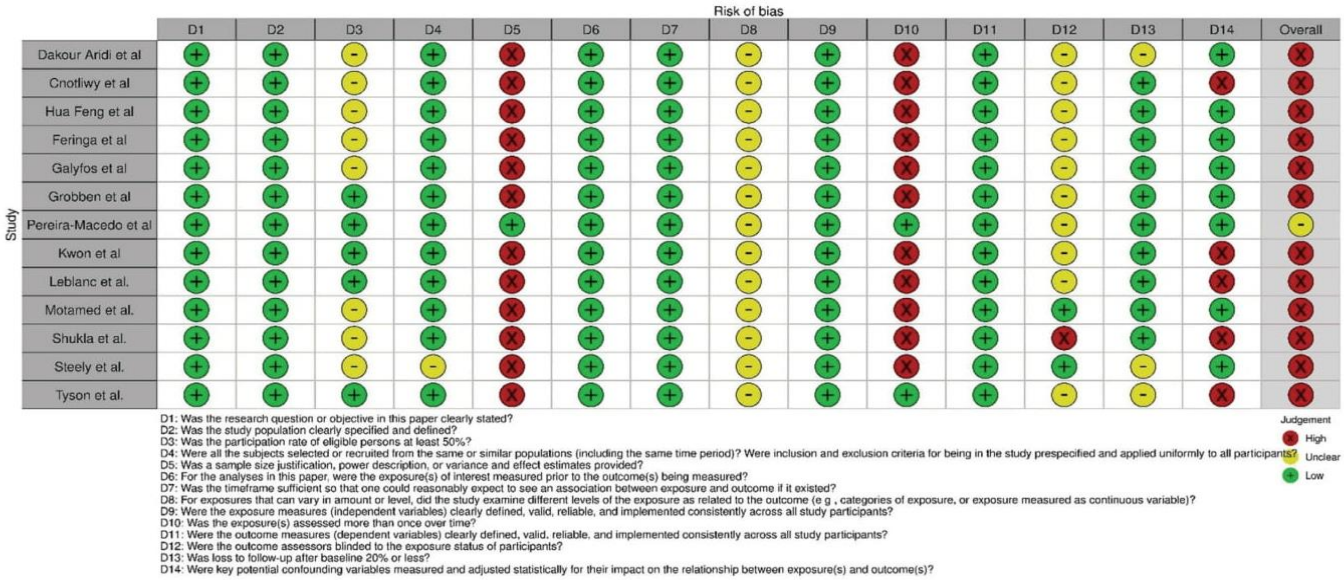

Figure 2. Risk of bias of all observational studies included in the systematic review, displayed by article.

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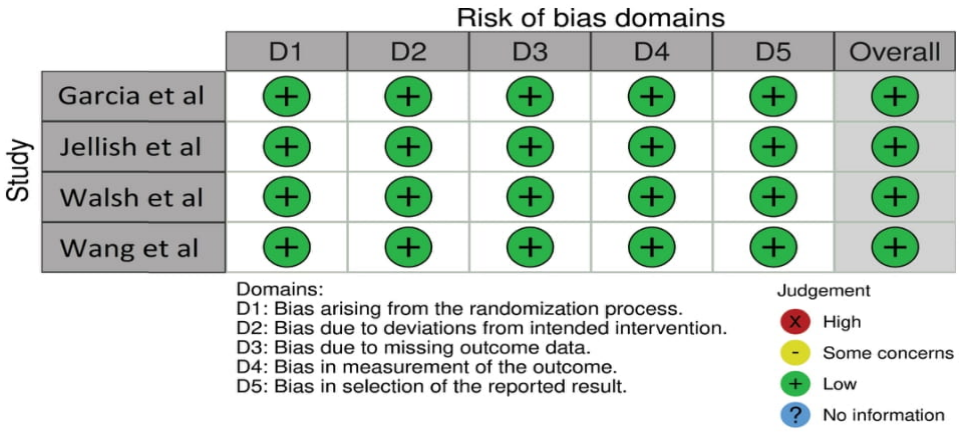
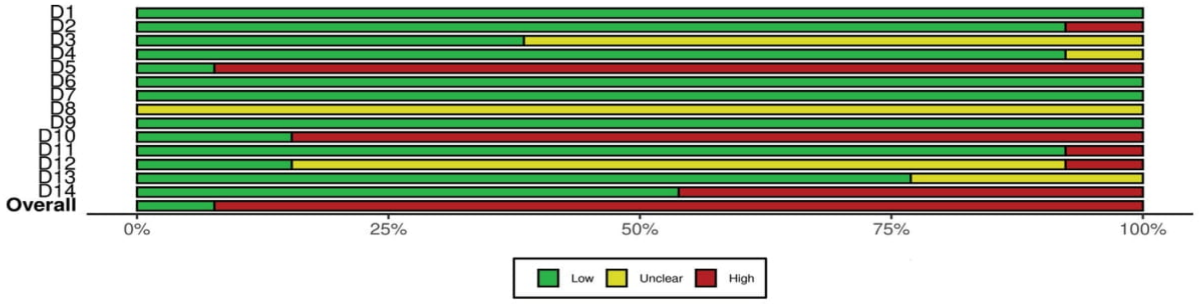


Figure 3. Risk of bias of included RCTs, displayed by article.



D1: Was the research question or objective in this paper clearly stated?
D2: Was the study population clearly specified and defined?
D3: Was the participation rate of eligible persons at least 50%?
D4: Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
D5: Was a sample size justification, power description, or variance and effect estimates provided?
D6: For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
D7: Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
D8: For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
D9: Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
D10: Was the exposure(s) assessed more than once over time?
D11: Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
D12: Were the outcome assessors blinded to the exposure status of participants?
D13: Was loss to follow-up after baseline 20% or less?
D14: Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and

Figure 4. Risk of bias of all included observational studies, displayed by item.

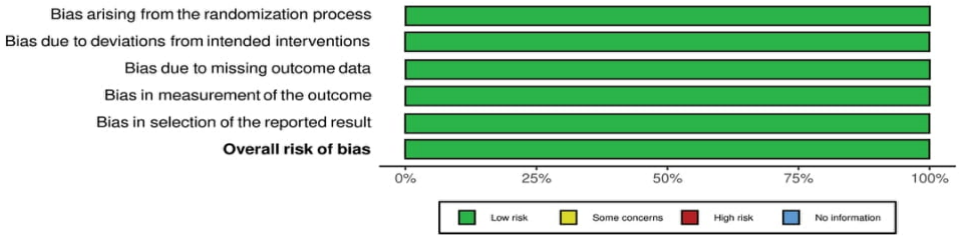


Figure 5. Risk of bias of all included RCTs, displayed by item.

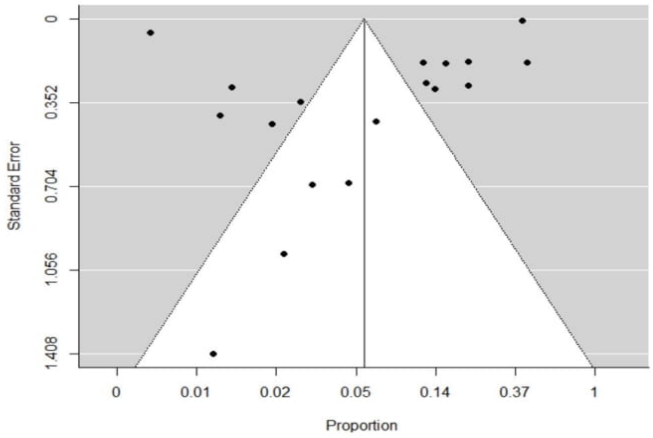


Figure 6. Funnel plot of publication bias assessment.

Conclusions

The incidence of MINS within 30-days after CEA ranged between 0% and 42.5% in the present systematic review. However, inferring results should be cautiously interpreted due to a significant heterogeneity amongst the selected studies and the diversity of study designs and methodology. Henceforward, additional research with a consistent and internationally defined methodology is required to provide valid results and assess the true incidence and risk factors of MINS in this subset of patients, with or without RA, as well as its appropriate management.

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DISCUSSION AND FUTURE PERSPECTIVES

DISCUSSION

Study Population

Patients undergoing CEA with RA in a tertiary referral center were enrolled in the study between January 2012 and January 2023. Patients presenting IND were prospectively and successively selected from this cohort database. The immediately consecutive patient without the occurrence of IND was selected as a control in a 1:1 ratio.

Evaluation before carotid surgery included vascular surgery and anesthesiology assessments. If the patient was presented with a positive symptomatic status, a neurologist was involved to detect any persistent sequelae that could be relevant for further comparison, which is in congruence with clinical guidelines (3). For CS diagnosis and degree stratification, patients were subjected to a duplex ultrasound, computed tomography angiography (111), or an additional duplex ultrasound executed by a distinct technician or physician. Patients were assessed postoperatively 30 and 90 days after hospital discharge and after 12 months subject to follow-up, with clinical examination and Doppler ultrasound. Other clinically relevant data, such as comorbidities and demography, were obtained through clinical registries and during surgery.

The presented studies of this thesis were reported according to STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) (112), Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis (TRIPOD) (113), and Developmental and Exploratory Clinical Investigations of DEcision support systems driven by Artificial Intelligence (DECIDE-AI) guidelines (114).

The Faculty of Medicine of the University of Porto′s Institutional Review Board (number 248-18) approved the studies on 14 July 2018 and the Ethics Committee waived informed consent. All studies respected the Declaration of Helsinki and are under the European Union General Data Protection Regulation (GDPR). The ongoing cohort was registered for patient enrolment at clinicaltrials.gov (NCTNCT04347785). This project did not comprise the assignment of patients to clinical or basic interventional settings.

Predictors of Intraoperative Neurologic Deficits and Clinical Importance of Patients Risk Stratification

The ability to predict IND during carotid clamping in CEA under RA is crucial because, despite being a soft outcome, it serves as a significant predictor of critical cerebral ischemia (56). Moreover, it was associated with increased rates of hard outcomes, including stroke (56, 88). Some ischemic lesions are associated with injury to the ischemic penumbra surrounding recent infarction and the traditional association between procedure-related embolization and intra- and postoperative stroke (29).

A body mass index (BMI) higher than 30 Kg/m^2 was found to be the main independent predictor, with a four-fold increased risk of IND during CACC (115). In the XGBoost model, obesity was the variable that had the greatest contribution to the outcome (116). Some theoretical and pragmatic explanations could be the reason for this uncommon association. It is not only associated with a higher prevalence of other comorbidities, but it also predisposes patients to worse surgical outcomes (117, 118). Obesity is associated with increased procedure duration, cardiac complications and mortality (119-121). In addition, obese patients present a greater tortuosity of the extracranial ICA (OR 1.59, 95% CI, 1.35–1.86; $p < 0.001$) that may be responsible for technical difficulties and a more extensive dissection, predisposing to cerebral hypoperfusion and embolic events (119-121). In a large cohort study with >25 000 patients submitted to CEA, metabolic syndrome was found to increase the odds of developing cardiocerebrovascular events (122). Increased body size in obese patients also affects stroke volume, predisposing to the thickening of the common carotid artery intima to compensate for luminal enlargement (122). Therefore, the common carotid artery diameter in this subset of patients could enhance hemodynamic stress (123). A shorter neck and a harder surgical

field may also contribute to increased clamping and respiratory intolerance (124). On another note, BMI > 30 Kg/m^2 was previously linked to carotid plaque instability, particularly in elderly male patients (125). Furthermore, the adipose tissue carries within itself a pro-inflammatory and atherosclerotic state by continuously inducing cytokines and macrophage activity, which is associated with poor outcomes (121, 126).

Even though the MICA score was created and validated to stratify patients according to their cardiovascular risk, evidence was still deficient regarding its effectiveness in predicting neurologic alterations (96). The present results demonstrated that the MICA score entailed significant interaction with the remaining risk factors (115). The higher the score, the greater the risk of IND (115). In another retrospective study with 540 717 patients who underwent non-cardiac surgery (12% were vascular interventions), MICA provided excellent results in predicting perioperative stroke, with a two-fold increased risk for patients with higher scores and an overall area under the curve (AUC) of 0.833 (0.825–0.842) (99). When analyzing the obtained AUC, a tendency was observed to favor the use of the MICA score over the previously created clinical model (115). Moreover, the value of the test is better perceived by its high negative predictive value (NPV), which translates to lower rates of false negatives, making it worthwhile to rule out IND events (115). Still, the detected tendency may have clinical relevance when considering the MICA score for patients' eligibility for CEA, relying on the potential comorbidities or underlying CS etiology.

Another significant result of this thesis is the strong contribution of the higher degrees of contralateral CS for IND incidence, in concordance with the authors' previous studies (57, 127). Many other studies have demonstrated that higher contralateral CS is associated with increased use of shunt in this subset of patients, corroborating the present findings (39, 128, 129). In fact, patients with contralateral stenosis or occlusion have been found

to present an increased risk of clamping intolerance and cerebral hypoperfusion (39). The GALA trial advocates a similar trend between contralateral disease and cerebrovascular events, whereas the literature extensively describes an increased perioperative stroke risk (43). The positive association between contralateral stenosis and IND has already been identified for other related outcomes, such as the increased risk of 30-day stroke or death, in-hospital strokes, and prolonged length of stay after CEA (42, 127, 130, 131). Another interesting finding is the relationship between the presence of contralateral CS and long-term all-cause mortality in CEA patients undergoing RA. Contralateral carotid occlusion has been primarily reported as a significant factor for 30-day stroke and death (132, 133). Bilateral carotid disease is also associated with underlying coronary artery disease, predisposing to higher rates of embolic events (134, 135).

For this reason, preoperative assessment of cardiac function may optimize surgical cardiac risks. Nevertheless, it remains within the recommended guidelines, not being an absolute contraindication for surgery (42, 127, 130, 131). With this in mind, the presence and degree of both ipsilateral and contralateral CS are crucial during patient selection and surgical planning for CEA (136). Moreover, CEA patients presenting polyvascular disease withhold a cumulative two-fold increased risk for long-term MACE and all-cause mortality (76). AMI and major adverse limb events were also postoperative outcomes in association with polyvascular disease (76). Considering the underlying pro-inflammatory nature of atherosclerosis, inherent endothelial dysfunction makes individuals more prone to cardiovascular events (137, 138).

Of a lesser magnitude, the presence of preoperative limb paresis implying previous cerebrovascular events in patients' history is associated with a higher risk of IND, calculated through the AI-developed model (139). The hemodynamic impairment, with critically hypoperfused arterial territories and compromised collateral pathways, may

explain these associations (140). Therefore, transient ischemic attacks and strokes may affect the blood mean velocity in the middle cerebral arteries and consequently exacerbate hemodynamic instability once a surgical intervention is performed (141).

Before multivariable analysis, the female gender was thought to play a role in inducing higher rates of IND, although this association was not confirmed (116). A possible explanation might be related to the low representation of females in the study sample, which could reduce the statistical power of this subgroup. Similar conflicting results regarding CEA outcomes were also supported in a community-based study, where crude significant differences among sex [female vs. male: Hazard Ratio 0.60 (95% CI 0.48–0.74)] were linked to the incidence of indication for CEA, but not after confounding adjustment [adjusted Hazard Ratio (aHR) 0.96 (0.76–1.22)] (142).

The use of the CRT analysis allowed for the establishment of patients' profiles based on the differentiating power, at various levels/generations, of the independent variables, explaining the distribution of IND incidence. By doing this, it was possible to determine MICA score cut-off points depending on the patient's profile/generation in the CRT and added further validity to the logistic regression model.

In conclusion, it is possible to state that the independent variable that primarily differentiates the occurrence or not of IND was obesity, with reduced influence of the independent variable contralateral CS for non-obese individuals.

Protective Factors

Increased levels of preoperative hemoglobin, platelets and a higher degree of ipsilateral stenosis demonstrated a protective role associated with fewer outcome events (116). Patients presenting a higher degree of ipsilateral CS apparently seem to be related to a decreased risk of IND (116). This finding may be explained by the increased compensatory collateral circulation mechanism impending from the contralateral carotid blood flow (111) and it is standardized solely in patients with unilateral CS (143). This adaptation is absent in patients with bilateral disease, where posterior circulation is thought to compensate for the decreased brain perfusion (143). For this reason, it is reasonable that a higher degree of contralateral CS is established as an independent risk factor for IND since it compromises this adjustment. On the other hand, the presence of an ipsilateral hypoperfusion state in more than 80% of patients with CS may also explain this finding (111, 144). It could be responsible for developing other adaptative mechanisms in chronic situations, leaving the patients with high-grade ipsilateral stenosis, especially for degrees above 90%, biologically better equipped to handle the ipsilateral CACC.

A higher hemoglobin level displayed a protective role in the incidence of IND in the XGBoost algorithm. Pothof et al. (130) conducted a large observational study of 16 068 patients submitted to CEA under GA and described a three-fold increased risk of 30-day mortality in symptomatic patients with preoperative anemia and decreased hematocrit. Meanwhile, the red cell distribution width – coefficient of variation (RDW-CV) hematologic parameter independently predicted MACE after CEA, as previously determined in another study (145). It has been described that higher plasma levels of inflammatory biomarkers are associated with the risk of cardiovascular events (146).

When patients are anemic, the impairment of oxygenation of cells occurring during CACC is facilitated. A trend of higher application of shunting was verified in the study for patients with anemia (130). No differences were found between symptomatic and asymptomatic disease (130). Another study reported that incremental decreased hemoglobin levels are associated with increased risk of perioperative stroke, MI, and death in patients undergoing CEA (147). Therefore, optimizing patients' hemoglobin parameters before surgery might be beneficial using conventional approaches, such as iron supplements or erythropoietin prescription (147).

Patients' profiles with increased levels of preoperative platelets are associated with fewer IND events (116). Studies have shown that platelet functions extend beyond their role in hemostasis, and they contain a variety of growth and trophic factors that influence brain function, holding considerable clinical importance (148). These factors play a role in the acceleration of the body's innate regenerative processes, which rely on neural stem cells, including neurogenesis and angiogenesis, and, therefore, contribute to neuronal protection (148, 149).

Carotid Shunting and Its Impact on Patient's Prognosis

During CACC, the ipsilateral hemisphere is hypoperfused, limiting blood flow and potentially leading to local thrombosis or direct neuronal lesion before a continuous flow is reestablished after shunting use (150). Promising results were recognized in several large clinical series (32, 89, 151). For example, in a meta-analysis by AbuRahma et al., 12 032 patients using a shunt presented perioperative stroke rates in the range of 0.7%–3.6% (32). On the other hand, the selective and routine non-shunter surgeons refute its use, backing their option with several reports stating that shunting might be dispensable in more than 85% of patients, therefore, avoiding underlying intercurrences, such as acute occlusion, arterial dissection, and air or thrombus emboli (34, 84, 152, 153).

In the present studies, carotid shunting alternatives in patients with IND might not play a substantial role in preventing these patients from important postoperative complications, although, due to several limitations, its benefit cannot be excluded (154). Findings have shown that a Clavien-Dindo score ≥ 2 or stroke risk were not statistically different between selective-shunt and non-shunt patients (control group) (154). These results are corroborated by previous works (36, 84, 155). An analysis of 3 800 CEA patients from the NSQIP database has supported that the association between carotid shunt and perioperative stroke or death was non-existent (P=0.34), under GA or RA (87% of them with GA vs. RA, P=0.55) (84). Kretz et al. also suggested that resorting to shunt did not positively impact short-term morbimortality (36). In fact, some findings have previously advocated a five and two-fold higher risk of carotid shunting in patients with contralateral carotid occlusion and severe kidney disease, respectively (155). Patch with a shunt has shown lower rates of Clavien-Dindo ≥ 2, compared to eversion or direct suture procedures, which were applied in non-shunt patients (154). However, after PSM

analysis, this association was not significant. No significant association with 30-day stroke was observed when both groups were compared. Gao et al., in a recent retrospective analysis of 653 patients undergoing CEA under GA for symptomatic status, could not validate the use of selective shunt in reducing MACE (155). A Cochrane meta-analysis with 1 270 patients from six RCTs demonstrated that carotid shunt was not associated with differences in death nor with stump pressure measurement, but then it showed a trend to a lower rate of 30-day stroke (OR 0.77, 95% CI 0.35–1.69) (31). Due to inconclusive findings, current guidelines recommend that the use of shunting should be left to the decision and experience of the operating surgeon (3). In addition, the results demonstrated that carotid shunt was not further associated with carotid restenosis (154). The actual evidence is scant and inconclusive (156). A common theory advocates that when a shunt is inserted, it might induce early myo-intimal hyperplasia, with further vessel stenosis (156). This potential association was previously studied by Cheng et. al (156), where 40% of 790 patients undergoing CEA were submitted to carotid shunting and the incidence of restenosis was also not confirmed (aHR: 0.83 95% CI 0.61–1.14, P = 0.25 and aHR: 0.96 95% CI 0.52–1.74, P = 0.88 for 50 and 70% stenosis grade, respectively), supporting the present results.

The Application of Machine Learning Models in the Prediction of Intraoperative Neurologic Deficits

By using machine learning, including a XGBoost model, it was possible to obtain a precise IND prediction in CEA, achieving an AUC of 0.82 (116). It was found that three clinical variables are associated with higher rates of IND in CEA patients under RA (116). Obese patients, the existence of high degrees of contralateral carotid stenosis and the presence of prior contralateral limb paresis or plegia were demonstrated to increase the risk of IND, being the former two of highest importance of contribution (116).

Concerning the XGBoost model, studies have demonstrated that it is a versatile machine-learning algorithm that predicts outcomes following CEA within the medical field and broader healthcare applications such as disease diagnosis, drug discovery, and patient risk assessment (102). It consistently outperforms alternatives like logistic regression, offering enhanced predictive accuracy with an AUC of 0.90 for 1-year stroke or death in CEA (102). XGBoost automates predictions from existing data despite potential integration complexities, simplifying complex clinical decisions (102). Its key strengths include robustness, efficient parallel processing, and handling of missing data, making it invaluable for optimizing patient care in several medical contexts (102). However, this method may entail an increased risk of overfitting (157), limiting the external validity of the results and, therefore, demanding larger cohorts assessments for additional validation.

The ability to find clinical patterns among patients prior to surgery might assist the surgeon in decision-making on the best approach to treat CS. Postoperative adverse outcomes in patients experiencing intraoperative IND demands delineating alternative treatment strategies. By predicting a potential intraoperative IND, the surgeon could consider transcarotid artery revascularization (TCAR) or transfemoral carotid stenting,

which is another viable approach without blood flow interruption by CACC (127, 158). TCAR might be a safe option for this population (127, 158). In fact, this surgical approach has demonstrated acceptable results, shorter surgical time, alongside comparable risks to those of CEA in regards to stroke and mortality (159). It has also demonstrated a lower risk of cranial nerve injury, even in patients presenting dynamic flow reversal for CS (159). Nonetheless, some preoperative factors, such as hemoglobin, platelets, and myocardial function, could be optimized before the intervention. A recent trial has demonstrated that targeted nutritional support might be beneficial in these patients to improve clinical and biochemical parameters and, therefore, achieve better outcomes (160).

Future research should involve larger and more diverse patient groups and collaboration across multiple centers.

Limitations

While the present thesis has offered valuable insights, it is essential to acknowledge the limitations of the studies. Thus, the study related to the role of the MICA score and application of the CRT model encompassed a sample size of under 200 individuals, mainly male, and from a single tertiary referral center. The specific sample recruited has a higher-than-usual event rate resulting from a selection of consecutive positive awake test patients, demanding a cautious interpretation of the results (115).

In the study related to shunt use, a smaller sample was achieved after PSM selection, and a lower number of patients with perioperative strokes were acknowledged, with an intrinsic limited statistical power (154). These limitations are also valid for AI-model algorithm studies (116), limiting the generalization of these findings. While carefully selecting and analyzing the sample, its size remained relatively small and case-control.

Furthermore, the recruitment had a long time frame due to the low rate of patients with CACC associated neurologic deficits, although the guidelines have not undergone significant changes regarding the indications for the study population (116). This could affect conclusions' statistical robustness and external validity, with some risk of overfitting the model due to the abnormal presence of events or IND. Therefore, multicenter and larger sample studies are required to confirm and validate the present results.

Moreover, patients admitted to a tertiary referral center are usually more endowed with significant comorbidities than those of peripheral centers, which may induce bias in interpreting results. Differences among surgical and anesthetic teams, such as experience and available techniques, were also not assessed.

The systematic review reporting worldwide MINS incidence after CEA is also not exempted from limitations (161). First of all, only a small number of articles were eligible for this systematic review. Most of the studies comprehended a small sample size without sample justifications and power descriptions, which led to a low precision of the obtained results. Additionally, despite having a low risk of bias, the included RCTs aimed to study different primary outcomes other than MINS, even though the authors have assessed MINS risk and underlying features.

On the other hand, the design of RCTs infers selection bias since patients are judiciously chosen to meet inclusion criteria. For instance, there was a severe heterogeneity amongst studies regarding baseline patient characteristics, study design, and methodology, prompting a multiversity of MINS definitions and troponin kits used. Actually, the differences between primary studies were so extensive that, in meta-regression, any single variable could be identified, which could possibly account for most of the heterogeneity. The multivariable meta-regression was not possible due to the insufficient number of included studies. Short- and long-term outcomes, such as stroke, AMI, MACE, or death, were assessed. However, only a few studies had them reported, which deprived the review of MINS association with other outcomes.

Future Perspectives

CS significantly impacts patient morbidity and mortality, making it a key focus in medical research fields. Current research has been directing efforts toward the impact of carotid revascularization on brain networking by navigating through radiologic features (162-164). In addition to the previous knowledge, cerebral imaging changes have been identified in relation to CS diagnosis (165-167). Magnetic Resonance Imaging (MRI), CT and electroencephalography methods were able to find that patients undergoing CEA may experiment global brain network rearrangements and an increase in regional neural adaptive activity (164, 168, 169). The presence of leukoaraiosis and widespread white-matter alterations (WMC) were previously identified as significant indicators of upcoming periprocedural cerebrovascular events and increased mortality risk (163, 164). The white-matter lesions seem to be related to underlying chronic cerebral hypoperfusion and microembolization as a result of CS and the inherent atherosclerosis process (170, 171). Nonetheless, higher grades of WMC are associated with plaque instability, making them more prone to emboli (164, 172). Age-related white matter changes (ARWMC) are also prevalent (above 90%) findings on MRI and CT in patients above 60 years old due to small vessel degenerative changes (173, 174). For these reasons, higher ratings of ARWMC and WMC have been described as significant predictors of ischemic stroke and MACE risks (175-177). Furthermore, in a previous study of 70 CEA patients, the amount of WMC was associated with the need for an intraoperative shunt (178). Hence, enhanced comprehension of brain imagiology with further enhancement with radiomics and neural networking adjustments would develop imaging scores that could play a primary role in predicting periprocedural neurologic deficit and stroke risk (177) and even how it could potentially address neurocognitive impairment in selected patients (179, 180).

This thesis did not assess the potential role of abnormalities of the circle of Willis (CoW) on IND incidence. It is a general belief that during extended CACC, the role of collateral pathways takes the lead in overcoming sudden blood flow interruption (181). Three-dimensional phase-contrast magnetic resonance imaging (3D PC-MRI) and time-of-flight (TOF) MR angiography (MRA) sequences constitute non-invasive methods capable of evaluating cerebral blood flow (182). The main difference between them lies in the fact that the former focuses primarily on flow and the latter analyses vascular anatomy. Some authors advocate that CoW-altered morphology on 3D TOF MRA is a significant risk factor for intraoperative cerebral ischemia during CACC (183). By using 3D PC MRI, the ability to predict patients at risk of IND was also observed in correlation with the predicted collateral pathways in the CoW (182). Myrcha et al. (153) suggests a combined analysis of intracranial arteries with magnetic resonance brain perfusion tests (P-MR) with acetazolamide and MRA to assist in detecting clamping intolerance during CEA. In a recent systematic review (184), no significant relation was found between deficient CoW and the occurrence of IND during CEA. However, available data in the review was insufficient to assess and discern more than a single CoW alteration that may predict IND, as formerly reported by many research groups (185-188). Considering this, preoperative planning perfusion MR techniques assessment of the CoW function and anatomical variations could be necessary for more accurate predictions and surgical plans. Moreover, larger samples and standardized definitions of CoW insufficiency are required for further detailed results.

From another perspective, postoperative stroke following CEA is mainly reported in association with thrombosis or embolism from the periprocedural zone (189). To the best of current knowledge, antiplatelet therapy has become paramount for all patients with atherosclerotic carotid disease since aspirin and clopidogrel can substantially reduce

cerebrovascular events risk (190). The beneficial effects of aspirin and clopidogrel are described in platelet activation, adhesion, and aggregation, contributing to atherosclerotic plaque stability (191). However, antiplatelet resistance was associated with increased rates of cerebral emboli and symptoms of brain hypoperfusion in patients with CS (192). Around 5.5%-61% and 4-30% of patients are resistant to aspirin and clopidogrel, respectively (193, 194). Increased platelet activity induces a higher risk of clamping intolerance, especially in symptomatic patients (195). Understanding the underlying mechanisms of platelet deposition in inducing postoperative stroke could dictate the best approach in tailoring antiplatelet drug therapy (195). This resistance may be classified as either clinical or laboratory-based. The latter is usually measured as continued platelet activity (195). In contrast, clinical resistance is related to therapy failure frequently caused by poor compliance, incorrect dose, drug interactions, or increased platelet turnover (195). Biochemical and genetic mechanisms may explain resistance development (193). Regarding aspirin, polymorphisms of the COX- 1/2 genes and thromboxane synthase are a potential cause of this failure (193, 196). Polymorphisms of the cytochrome P450 family have been identified in relation to clopidogrel's resistance (193, 196-198). Hence, the identification of patients lacking sufficient response to antiplatelet therapy is essential to optimize the perioperative period in CEA (199). Identifying specific pathways responsible for inducing platelets' activation response may allow tailored antiplatelet treatments by achieving an optimized control between thrombosis and hemostatic risks.

CONCLUSIONS

The created XGBoost model achieved an AUC of 0.82 for predicting IND.

Several clinical findings seem to play an essential role in predicting IND in patients undergoing CEA with RA: higher BMI rates, increased degree of contralateral carotid stenosis, and limb paresis or plegia. Protective laboratory features such as higher preoperative platelets and increased hemoglobin levels were also identified. A higher degree of ipsilateral carotid stenosis reduces the risk of IND.

AI tools allow the identification of increased risk patients' profiles that may assist the surgeon in tailoring the best approach for patients fulfilling those mentioned above clinical and biochemical issues.

MICA risk score might play a role in the preoperative period of CEA, stratifying patients for the occurrence of IND in CEA and consequently for worse surgical outcomes. The created predictive model with MICA has provided the ability to better rule out the event with an NPV of 97%.

In addition, obesity was shown to be the most dominant discriminating factor, followed by a MICA score above 8 points. For non-obese patients, a MICA score of 10, together with contralateral stenosis of at least 55%, was also discriminative. A higher degree of ipsilateral stenosis is suggested to have a part in preventing procedure-related IND.

Incidence of perioperative stroke or further complications (Clavien–Dindo ≥ 2) did not demonstrate significant reduction when shunting was applied during CACC in patients submitted to CEA under RA, with a positive awake test.

The incidence of MINS within 30 days after CEA ranged between 0% and 42.5% in the present systematic review. However, inferring results should be cautiously interpreted

due to a significant heterogeneity among the selected studies and the diversity of study designs and methodology. Further studies in carotid surgery, with larger samples, are needed to assess the real benefit of the MICA score in predicting IND and stroke.

Additionally, research on the risk score for ultra-selective prophylactic shunting or on other strategies to prevent and reduce the development of IND is required to improve perioperative outcomes. Further application of the AI model in larger samples is necessary to validate these findings.

MAIN FINDINGS

- The created AI XGBoost model achieved an AUC of 0.82. The features that were identified as predictors were higher BMI levels, an increased degree of contralateral CS, and limb paresis or plegia.
- Higher preoperative platelets and hemoglobin levels have a protective role.
- A higher degree of ipsilateral carotid stenosis reduces the risk of IND.
- MICA score may have a role in stratifying patients according to their probability of developing intraoperative neurologic deficits.
- A MICA score of at least eight in obese patients has a negative predictive value of 97% and is the most significant discriminative factor when developing intraoperative neurologic deficits.
- A MICA score of 10 with contralateral stenosis of at least 55% is another significant discriminative profile for non-obese patients.
- Resorting to shunting did not demonstrate an advantage regarding 30-day stroke or a Clavien–Dindo ≥ 2 rates.
- The incidence of MINS within 30 days after CEA ranged between 0% and 42.5% in the systematic review.

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