Original article

doi:10.5633/amm.2025.0319

Predictive Factors for Major Adverse Cardiac Events After Carotid Endarterectomy

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Carotid endarterectomy (CEA) is a standard surgical procedure for stroke prevention in patients with carotid artery stenosis but carries a significant risk of major adverse cardiovascular events (MACE). By integrating these biomarkers, we aim to improve preoperative risk stratification and contribute to the development of personalized perioperative care strategies in this high-risk patient population.

A total of 110 patients undergoing elective CEA in 2017 were prospectively enrolled. Preoperative clinical data, including suPAR, urea, and LVEF, were collected. MACE—defined as myocardial infarction, arrhythmias, heart failure, stroke, or cardiovascular death—was monitored for 30 days postoperatively. Statistical analysis included univariate and Cox regression modeling to assess predictors of MACE.

Within 30 days post-CEA, 10 patients (9.1%) experienced MACE. These patients had significantly higher suPAR levels (7.04 ± 1.81 vs. 3.15 ± 1.01 ng/mL, $p < 0.001$), elevated serum urea (7.69 ± 2.25 vs. 6.14 ± 1.89 mmol/L, $p = 0.024$), and lower LVEF (48.9 ± 5.43% vs. 55.17 ± 7.8%, $p = 0.007$). Cox regression analysis identified suPAR as an independent predictor of 30-day MACE (HR = 2.144, $p < 0.001$).

Elevated preoperative suPAR, increased serum urea, and reduced LVEF are associated with higher risk of MACE following CEA. Integrating these biomarkers into preoperative assessment may enhance cardiovascular risk stratification and guide perioperative management in high-risk patients.

Keywords: Carotid endarterectomy;MACE;suPAR;Ejection fraction;Urea.

Originalni rad

doi:10.5633/amm.2025.0319

Prediktivni faktori za velike neželjene srčane događaje nakon karotidne endarterektomije

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Karotidna endarterektomija (CEA) predstavlja standardnu hirurško proceduru u prevenciji moždanog udara kod pacijenata sa stenozom karotidne arterije, ali nosi značajan rizik od nastanka velikih neželjenih kardiovaskularnih događaja (MACE).

Cilj rada je unaprediti preoperativnu procenu rizika i doprineti razvoju personalizovanih perioperativnih strategija kod ove populacije sa visokim rizikom.

U studiju je tokom 2017. godine prospektivno uključeno ukupno 110 pacijenata podvrgnutih elektivnoj CEA. Prikupljeni su preoperativni klinički podaci, uključujući nivoe suPAR, uree i LVEF. MACE — definisani kao infarkt miokarda, aritmije, srčana slabost, moždani udar ili kardiovaskularna smrt — praćeni su tokom 30 dana nakon operacije. Statistička analiza je uključivala univarijantnu analizu i Koksovu regresiju radi procene prediktora MACE.

Tokom 30 dana nakon CEA, MACE su se javili kod 10 pacijenata (9,1%). Ovi pacijenti su imali značajno više nivoe suPAR-a (7,04 ± 1,81 naspram 3,15 ± 1,01 ng/mL, $p < 0,001$), povišene vrednosti uree (7,69 ± 2,25 naspram 6,14 ± 1,89 mmol/L, $p = 0,024$), i nižu LVEF (48,9 ± 5,43% naspram 55,17 ± 7,8%, $p = 0,007$). Koksova regresiona analiza je identifikovala suPAR kao nezavisan prediktor za pojavu MACE u roku od 30 dana (HR = 2,144, $p < 0,001$).

Povišeni preoperativni nivoi suPAR-a, povećana urea i smanjena ejekciona frakcija povezani su sa većim rizikom od MACE nakon CEA. Integracija ovih biomarkera u preoperativnu procenu može unaprediti stratifikaciju kardiovaskularnog rizika i pomoći u planiranju perioperativnog menadžmenta kod pacijenata visokog rizika.

Ključne reči: Karotidna endarterektomija; MACE; suPAR; Ejekciona frakcija; Urea.

PREDICTIVE FACTORS FOR MAJOR ADVERSE CARDIAC EVENTS AFTER CAROTID ENDARTERECTOMY

Introduction

Carotid endarterectomy (CEA) is a commonly performed surgical intervention aimed at reducing the risk of stroke in patients with significant carotid artery stenosis (1). As the aging population continues to grow and surgical techniques advance, the frequency of major vascular procedures such as CEA has increased substantially, particularly among elderly patients (2). Despite its benefits, CEA remains associated with notable perioperative cardiovascular risk (3). According to the European Society of Cardiology (ESC) and the European Society of Anaesthesiology and Intensive Care (ESAIC), major vascular surgery is classified as high-risk due to the elevated incidence of perioperative myocardial infarction and cardiac arrest, which exceeds 5% in this population (4). Given that atherosclerosis is a systemic and progressive disease, fewer than 10% of patients undergoing major vascular surgery present with angiographically normal coronary arteries (5). This underscores the critical need for comprehensive cardiovascular risk assessment in the perioperative s

Cardiac biomarkers play a pivotal role in the evaluation and prognostication of patients undergoing CEA. The identification of patients at heightened risk for myocardial injury and major adverse cardiovascular events (MACE) — a composite endpoint encompassing cardiovascular death, myocardial infarction, stroke, and heart failure — is essential for optimizing clinical outcomes (6). In recent years, both conventional and novel biomarkers have been investigated to enhance the precision of preoperative risk stratification.

Among these, soluble urokinase plasminogen activator receptor (suPAR) has emerged as a promising candidate. suPAR is a stable circulating marker that reflects chronic immune activation and systemic inflammation — key processes implicated in the pathophysiology of atherosclerosis (7). Elevated suPAR levels have been associated with adverse cardiovascular outcomes in various clinical settings, suggesting potential utility in identifying patients at increased risk for postoperative complications (8). In addition to suPAR, traditional markers such as serum urea — an indicator of renal function and systemic catabolic stress — and left ventricular ejection fraction (LVEF), a widely used measure of cardiac performance, may also contribute valuable prognostic information in the context of vascular surgery (9,10).

Early and accurate identification of high-risk patients could enable more tailored perioperative management, thereby reducing the incidence of MACE and improving long-term prognosis (11). However, data on the combined predictive utility of suPAR, urea, and LVEF in patients undergoing CEA remain limited.

Therefore, the objective of this study is to evaluate the predictive value of preoperative suPAR levels, serum urea, and LVEF in identifying patients at increased risk for MACE following carotid endarterectomy.

Aim of study

By integrating these biomarkers, we aim to improve preoperative risk stratification and contribute to the development of personalized perioperative care strategies in this high-risk patient population.

Material and methods

The study was approved by the Ethics Committee of Medical Faculty University of Nis, Serbia. During 2017, we prospectively enrolled all 110 patients prepared for major open elective vascular surgery - carotid endarterectomy in Clinic for Cardiovascular and Transplantation Surgery, Clinical Center Niš, Niš, Serbia. Exclusion criteria were: 1) patients younger than 21 years, 2) unstable coronary disease and 3) decompensated heart failure. All procedures were performed during general anesthesia. All patients initially underwent detail evaluation of medical history, physical examination, routine hematologic and biochemical blood analysis, 12-lead electrocardiogram, and chest radiography. We used online risk calculator software for V-POSSUM (http://www.riskprediction.org.uk/vascindex.php). During the 30-days after the procedure, major adverse cardiac events such as: myocardial infarction, ventricular arrhythmias, decompensating heart failure, and new onset atrial fibrillation were recorded

Statistical Analysis

The collected data were analyzed using standard descriptive statistical parameters, including arithmetic mean, standard deviation, minimum and maximum values, absolute numbers, and relative frequencies (percentages). Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Numerical variables were compared between two groups using the t-test or Mann-Whitney U test, depending on data distribution. Cox regression analysis was employed for survival analysis. The null hypothesis was tested at a significance level of $\alpha = 0.05$. Statistical analyses were conducted using the R statistical software package.

Results

A total of 110 patients were included in the study (54 males and 56 females). The mean age of the study population was 67.43 ± 5.62 years (range: 48–79 years). A history of prior stroke was reported in 44.5% of patients, while diabetes mellitus (DM) was present in 35.5%. Most patients were receiving beta-blockers (77.3%) and ACE inhibitors (65.5%) (Table 1).

Table 1. Demographic and Clinical Characteristics of the Study Population

Variable	N (%) / Mean ± SD	Range
Age†	67.43 ± 5.62	48–79
Sex		
– Male	54 (49.1%)	49,1
– Female	56 (50.9%)	50,9
Atrial fibrillation	3 (2.7%)	2,7
Prior stroke	49 (44.5%)	44,5
Coronary artery disease	21 (19.1%)	19,1
Cardiomyopathy	11 (10.0%)	10,0
Prior PCI	4 (3.6%)	3,6
Prior myocardial infarction	18 (16.4%)	16,4
Prior CABG	1 (0.9%)	0,9
Diabetes mellitus	39 (35.5%)	35,5
Insulin-dependent DM	22 (20.0%)	20,0
Hyperlipidemia	20 (18.2%)	18,2
Smoking	36 (32.7%)	32,7
Positive family history	37 (33.6%)	33,6
Beta-blockers	85 (77.3%)	77,3
ACE inhibitors	72 (65.5%)	65,5
Calcium channel blockers	24 (21.8%)	21,8
Antithrombotic therapy	57 (51.8%)	51,8
Statins	62 (56.4%)	56,
Diuretics	24 (21.8%)	51,8
Nitrates	8 (7.3%)	7,3

† Mean ± Standard Deviation, Minimum–Maximum

Within the first 30 postoperative days, 10 patients (9.1%) experienced a MACE (major adverse cardiovascular event). These included: 4 myocardial infarctions, 4 ventricular arrhythmias, 3 cardiopulmonary resuscitations, 6 episodes of decompensated heart failure, 4 new episodes of atrial fibrillation, 1 stroke, and 1 neurological complication.

Coronary artery disease and prior PCI were significantly more common in patients who experienced MACE within the first 30 days ($p = 0.021$ and $p = 0.041$, respectively). Conversely, a history of stroke was significantly more frequent among those who did not experience an event ($p = 0.040$). Antithrombotic therapy was significantly more common among patients who developed MACE ($p = 0.017$). Additionally, MACE frequency differed significantly based on the severity of dyspnea ($p = 0.029$). There was no significant association between ASA score and MACE occurrence ($p = 0.334$) (Table 2).

Table 2. Demographic and Clinical Characteristics by 30-Day MACE Status

(Selected rows shown for brevity)

Variable	No Event (N, %)	MACE (N, %)	P
Age	67.27 ± 5.63	69.00 ± 5.52	0.356[2]
Sex (Male)	49 (49.0%)	5 (50.0%)	1.000[1]
Prior stroke	48 (48.0%)	1 (10.0%)	0.040
Coronary artery disease	16 (16.0%)	5 (50.0%)	0.021
Prior PCI	2 (2.0%)	2 (20.0%)	0.041
Antithrombotic therapy	48 (48.0%)	9 (90.0%)	0.017
NYHA Class III	23 (23.0%)	6 (60.0%)	0.029

[1] Fisher's exact test; [2] t-test

Patients who experienced MACE within the first 30 days showed significantly higher levels of urea ($p = 0.024$), sUPAR ($p < 0.001$), and lower left ventricular ejection fraction (LVEF) ($p = 0.007$) compared to those without events (Table 3).

Table 3. Laboratory Parameters by 30-Day MACE Status

Variable	No Event	MACE	P
Urea (mmol/L)	6.14 ± 1.89	7.69 ± 2.25	0.024
sUPAR (ng/mL)	3.15 ± 1.01	7.04 ± 1.81	<0.001
LVEF (%)	55.17 ± 7.8	48.9 ± 5.43	0.007

*Mann-Whitney U test

Table 4. Cox Regression Analysis of Predictors for 30-Day MACE

Variable	B	HR	95% CI	p
Age	0.026	1.027	0.887–1.188	0.725
Sex	-0.308	0.735	0.154–3.514	0.700
ASA Score	-0.558	0.572	0.067–4.884	0.610
Urea	0.159	1.172	0.850–1.616	0.333
sUPAR	0.763	2.144	1.561–2.944	<0.001
NYHA III	-0.078	0.925	0.105–8.114	0.944

*B – Regression coefficient; HR – Hazard Ratio; 95% CI – 95% Confidence Interval

Cox regression analysis demonstrated that elevated preoperative sUPAR levels were significantly associated with the occurrence of MACE within 30 days (HR: 2.144, $p < 0.001$). No significant associations were found for age, sex, ASA score, or NYHA class (Table 4).

Discussion

The interpretation of major adverse cardiovascular events (MACE) in the context of carotid endarterectomy (CEA) remains complex due to the lack of a standardized and universally accepted definition. While MACE is commonly defined as a composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, considerable heterogeneity exists across studies. Some definitions additionally include heart failure, arrhythmias, urgent revascularization, or hospital readmission (12). This variability hinders direct comparison between studies and complicates meta-analytic interpretations. Moreover, inconsistencies in outcome timeframes (e.g., 30-day vs. long-term) and diagnostic methods further obscure comparability. Given the dual cerebrovascular and cardiovascular risks associated with CEA, a procedure-specific, harmonized MACE definition is warranted to improve evidence-based perioperative care.

by age In our cohort, the mean patient age was 67.4 ± 5.6 years—reflective of an inherently high-risk population. Age is a well-established predictor of perioperative complications, due in part to increased arterial stiffness, decreased physiologic reserve, and a higher prevalence of comorbid conditions such as coronary artery disease (CAD), atrial fibrillation (AF), and heart failure (13,14). A meta-analysis by Nantakool et al. showed significantly increased rates of stroke, myocardial infarction, and mortality in patients ≥75 years, especially among octogenarians (15). These outcomes are likely driven -related endothelial dysfunction, frailty, and impaired autonomic regulation.

Our population exhibited a high burden of comorbidities—most notably, a history of cerebrovascular events in 44% of patients. Such patients are at increased risk for cerebral hypoperfusion and impaired autoregulation, making them more susceptible to perioperative ischemia (16). Additionally, patients with previous ischemic heart disease and prior percutaneous coronary intervention (PCI) were overrepresented among those who developed MACE. Although PCI is intended to stabilize coronary pathology, it is also a marker of advanced atherosclerosis and residual ischemic burden, and it introduces complexities related to dual antiplatelet therapy and perioperative bleeding risk (17).

Interestingly, patients receiving antiplatelet therapy had a higher incidence of MACE, which may reflect confounding by indication—i.e., antiplatelets being prescribed more frequently to those with established cardiovascular disease (18). This emphasizes the need for careful interpretation of medication effects in observational studies.

Postoperative arrhythmias—especially atrial fibrillation—were among the most frequent complications, consistent with existing literature (19). Pathophysiologic drivers include hemodynamic stress, autonomic imbalance, and systemic inflammation. Elderly patients with structural heart disease are particularly vulnerable. We also observed cases of ventricular arrhythmia and three instances requiring cardiopulmonary resuscitation, highlighting the severity of cardiac events following CEA. Previous reports by Hertzer et al. and Hannan et al. identified arrhythmias as independent predictors of perioperative morbidity and mortality (20,21).

Diabetes mellitus, present in 35.5% of our cohort, was another significant contributor to adverse outcomes. Diabetic patients exhibit endothelial dysfunction and systemic inflammation, both of which increase susceptibility to ischemia and adverse cardiovascular events (22). Pharmacologic management, including beta-blockers and ACE inhibitors, was prevalent. While beta-blockers are known to reduce sympathetic activity and prevent ischemia, their association with cerebral hypoperfusion and increased intraoperative shunting has been reported (23). The role of ACE inhibitors remains debated, though some studies suggest perioperative benefits in stroke and mortality reduction (24).

Among novel risk markers, soluble urokinase plasminogen activator receptor (suPAR) and serum urea have emerged as promising biomarkers. Elevated preoperative suPAR levels reflect systemic immune activation and are associated with increased risk of adverse outcomes in vascular surgery (25,26). Its stability and chronic disease sensitivity make it an attractive tool in risk stratification. Likewise, elevated serum urea—indicative of renal dysfunction and catabolic stress—has been independently linked with increased postoperative myocardial infarction, stroke, and death (27).

Our findings also validated the utility of the NYHA functional classification, as higher NYHA classes were associated with increased MACE risk. NYHA status reflects the extent of heart failure symptoms and functional capacity, both of which are critical in predicting cardiovascular vulnerability in the perioperative period (28).

Left ventricular ejection fraction (EF), another cornerstone of cardiovascular evaluation, was a robust predictor in our study. Reduced EF (<40%) significantly correlated with higher rates of MACE, including myocardial infarction and arrhythmias. LV dysfunction signals poor myocardial reserve and electrical instability, mandating optimized pharmacologic therapy and hemodynamic management in the perioperative setting (29).

In conclusion, our findings underscore the multifactorial nature of cardiovascular risk in patients undergoing CEA. Advanced age, comorbid burden, arrhythmias, and emerging biomarkers such as suPAR and urea collectively inform risk stratification. A comprehensive, individualized approach—combining clinical history, functional classification, and biomarkers—is critical for improving outcomes in this high-risk population.

Conclusion

Major adverse cardiovascular events (MACE) remain a significant cause of morbidity and mortality following carotid endarterectomy (CEA), underscoring the need for improved perioperative risk stratification. Our findings support the utility of a multimodal biomarker approach incorporating soluble urokinase plasminogen activator receptor (suPAR), serum urea, and left ventricular ejection fraction (LVEF) as a means of identifying patients at elevated cardiovascular risk. Each of these markers offers distinct yet complementary insights into the pathophysiological processes underlying postoperative complications—chronic inflammation, renal dysfunction, and impaired cardiac performance.

suPAR serves as a robust indicator of systemic inflammatory burden and atherosclerotic disease activity, while elevated serum urea reflects metabolic stress and possible cardiorenal dysfunction. Reduced LVEF, a well-established predictor of adverse cardiac outcomes, highlights underlying myocardial vulnerability. The integration of these parameters into a unified risk assessment model may enhance the precision of perioperative management strategies and improve patient outcomes.

Further prospective studies are warranted to validate this triad of biomarkers and evaluate its performance in predictive algorithms tailored to the CEA population. Ultimately, such an approach may facilitate personalized perioperative care, enabling timely interventions that mitigate the risk of cardiovascular complications in high-risk surgical patients.

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