Carotid calcium burden and perivascular fat density on computed tomography angiography as predictors of outcomes after carotid endarterectomy

Martha M. C. Koek, MD, MSc,[a] Mario D'Oria, MD,[b] Franziska Röder, BSc,[a] Reinoud P. H. Bokkers, MD, PhD,[c] Robert A. Pol, MD, PhD,[d] Maarten Uyttenboogaart, MD, PhD,[c,e] Sandro Lepidi, MD,[b] Riccardo Rebuzzi, MD,[b] Jean-Paul P. M. de Vries, MD, PhD,[a] Richte C. L. Schuurmann, MD, PhD,[a] *and* Clark J. Zeebregts, MD, PhD,[a] *Groningen, the Netherlands; and Trieste, Italy*

ABSTRACT

Objective: Atherosclerotic disease of the extracranial internal carotid artery affects over 1.5% of the global population and poses major health risks, including ischemic stroke and mortality. Although carotid endarterectomy (CEA) reduces these risks, it carries a 2% to 6% risk of major complications. Improved risk stratification beyond stenosis severity is needed. This study aimed to evaluate whether the carotid calcium score, as a marker of plaque stability, and perivascular fat density, as a marker of inflammatory activity, independently predict clinical outcomes after CEA. The assessed outcomes included all-cause mortality, cardiovascular mortality, major adverse cardiac events (MACE), neurological events, and restenosis.

Methods: This single-center retrospective cohort study included 178 patients who underwent CEA between 2015 and 2021 and had preoperative computed tomography angiography within 6 months of surgery. The modified Agatston calcium score was calculated bilaterally using patient-specific attenuation thresholds, and perivascular fat density (Hounsfield units) was measured in standardized regions of interest. Statistical analysis included correlation testing, Kaplan-Meier survival analysis, and Cox proportional hazard models.

Results: Preoperative imaging biomarkers (stenosis degree, calcium score, and fat density) were not interrelated and did not predict early postoperative complications. However, lower calcium scores were associated with improved long-term outcomes, including lower risk of MACE ($P = .041$) and lower cardiovascular mortality ($P = .023$). At 4 years, survival for all-cause mortality was higher in the low calcium group (63.6% vs 58.0%, $P = .008$). In asymptomatic patients, differences were even greater for MACE (79.3% vs 48.1%; $P = .005$) and all-cause mortality (78.2% vs 54.9%; $P = .004$). The carotid calcium score independently predicted the risk of MACE (hazard ratio [HR] = 1.63; 95% confidence interval [CI]: 1.15-2.33; $P = .007$) and cardiovascular mortality (HR = 3.12; 95% CI: 1.01-9.58; $P = .047$), after adjustment for confounding variables. Higher fat density was associated with increased risk of restenosis (HR = 5.69; 95% CI: 1.18-27.4; $P = .030$), though this was not an independent predictor.

Conclusions: High ipsilateral carotid artery calcium score independently predicted the risk of MACE and cardiovascular mortality after CEA and was associated with a trend toward increased all-cause mortality up to 4 years of follow-up. Predictive values were even stronger in asymptomatic patients. Perivascular fat density seems to be relevant to predict restenosis. These plaque characteristics may help identify patients most likely to benefit from CEA and those who may require intensified postoperative cardiovascular risk management due to elevated complication risk. (J Vasc Surg 2025;82:2079-89.)

Keywords: Carotid artery diseases; Endarterectomy; Carotid; Calcium; Adipose tissue; Risk assessment

From the Department of Surgery, Division of Vascular Surgery, University Medical Center Groningen, University of Groningen, Groningen[a]; the Division of Vascular and Endovascular Surgery, Department of Clinical Surgical and Health Sciences, University of Trieste, Trieste[b]; and Department of Radiology,[c] Department of Surgery, Division of Transplantation,[d] and Department of Neurology,[e] University Medical Center Groningen, University of Groningen, Groningen.

Correspondence: Clark J. Zeebregts, MD, PhD, Department of Surgery, Division of Vascular Surgery, University Medical Center Groningen, University of Groningen, Hanzeplein 1, Groningen 9713 GZ, the Netherlands (e-mail: c.j.a.m.zeebregts@umcg.nl).

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Atherosclerotic disease of the extracranial carotid artery with stenosis >50% affects approximately 1.5% of the global population aged 30-79 years.[1] Stroke is the leading cause of long-term disability and the third leading cause of death worldwide. Of all strokes, 87% are ischemic, with 20% attributed to carotid artery stenosis.[2-4] In patients with asymptomatic carotid stenosis greater than 70%, the 5-year risk of ischemic stroke is up to 4.7% without intervention.[5] In addition to best medical treatment and risk factor management, carotid endarterectomy (CEA) or carotid artery stenting (CAS) are treatment options. CEA carries a 2% to 6% risk of any complications.[6] For symptomatic patients with 70% to 99% stenosis, the number needed to treat to prevent one ipsilateral cerebral event is 6, whereas this

number increases to 20 for those with 50% to 69% stenosis.[7] Given the inherent risks of carotid surgery, the decision to proceed can cause considerable uncertainty and stress for patients. More reliable predictors could support the decision-making process for CEA, or CAS as a less invasive alternative, and help tailor follow-up care through appropriate cardiovascular risk management.

Currently, individual risk can be estimated using risk stratification tables or algorithms, such as the Carotid Artery Risk score, which is based on several variables including the degree of stenosis.[8,9] However, plaque characteristics may also be critical in predicting outcomes after CEA. Several markers of plaque instability have been identified as independent risk factors for recurrent transient ischemic attack or stroke.[10-13] The role of calcification in plaque vulnerability remains debated. Although higher calcium scores suggest more stable, fibrotic plaques, they also reflect a more advanced stage of atherosclerotic disease.[14-16] Because calcium scoring with the Agatston method is well established in the assessment of coronary artery disease, a modified Agatston carotid calcium score could help improve patient selection for carotid surgery and reduce postoperative complications.[17,18]

In addition to calcification, perivascular fat located immediately outside the adventitia has emerged as a potential imaging biomarker for vascular inflammation rather than merely a passive indicator of fat density. Perivascular adipose tissue plays a dynamic role in vascular biology: under normal conditions, it exerts protective paracrine effects, but in disease states, it can become dysfunctional and proinflammatory. Factors such as obesity, diabetes mellitus (DM), aging, and systemic inflammation contribute to this shift.[19] Inflammatory changes in perivascular fat are associated with increased release of cytokines and reactive oxygen species, which can accelerate atherosclerosis and impair vascular healing.[20] Computed tomography (CT)-derived fat attenuation, expressed in Hounsfield units (HU), has been proposed as a surrogate for this inflammation, with higher values reflecting more inflamed, lipid-depleted fat.[21]

The aim of this study was to evaluate the predictive value of two imaging biomarkers derived from CT: the carotid calcium score and the perivascular fat density, for various clinical outcomes in patients after CEA, while also validating and strengthening the findings of the pilot study by Röder et al.[22]

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective cohort study
- **Key Findings:** At a median follow-up of 4 years after carotid endarterectomy in 178 patients with significant stenosis (>50%), cardiovascular mortality was 3.4%, major adverse cardiac events occurred in 25.3%, and restenosis was observed in 5.6%. A high carotid calcium score on computed tomography angiography independently predicted cardiovascular mortality and major adverse cardiac events. In asymptomatic patients, this association was even stronger and extended to all-cause mortality. Higher perivascular fat density showed a trend toward increased risk of restenosis.
- **Take Home Messages:** Carotid calcium score is a promising marker of carotid plaque characteristics and may help guide individualized treatment before and after carotid endarterectomy.

METHODS

Study design. This single-center, retrospective observational cohort study included consecutive patients who underwent elective CEA at the Hospital of Trieste between 2015 and 2021, and had a preoperative CT angiogram performed within 6 months before surgery. Data analysis was performed at the University Medical Center Groningen. Patients aged ≥18 years were eligible; both symptomatic and asymptomatic patients were included. Exclusion criteria were CT scans performed more than 6 months before surgery, concomitant coronary artery bypass grafting, prior ipsilateral or contralateral CEA, or prior ipsilateral or contralateral CAS. The hospital in Trieste, Italie, was responsible for ensuring that patient data were collected and shared in accordance with their national regulations. The interhospital data sharing agreement includes provisions to ensure compliance with ethical and legal standards in both countries. In the Netherlands, the study was approved by the University Medical Center Groningen Medical Ethical Review Board (METc 2024/140) and conducted in accordance with the Declaration of Helsinki. As the study did not fall under the Dutch Medical Research Involving Human Subjects Act (WMO), additional informed consent was not required.

Data collection. CT-scan data were securely transferred to the Netherlands in accordance with the interhospital data sharing agreement. Clinical data were retrospectively collected from patient records in 2024, including demographics, comorbidities, medication use, laboratory values, and disease-specific characteristics such as the side and degree of stenosis, presence of symptoms, and any complications. Early complications (cerebrovascular events, cranial nerve palsy, postoperative bleeding, and myocardial infarction) were defined as events occurring within 30 days postoperatively. Long-term complications were tracked until death, loss of follow-up, or the end of the study's follow-up period. These included ipsilateral neurological events (stroke, transient ischemic attack, and amaurosis fugax),

major adverse cardiovascular events (MACE: myocardial infarction, unstable angina pectoris, and heart failure), all-cause mortality, cardiovascular mortality, and restenosis (defined as ≥50% stenosis on duplex ultrasound examination). Follow-up ranged from 3 to 9 years, with a median of 53 (interquartile range [IQR]: 41-67) months.

CT-scan analysis. Preoperative contrast-enhanced CT scans were acquired using five scanners at the Italian center: Philips iCT 256 (n = 110), Siemens Somatom Definition AS+ (n = 31), GE LightSpeed Pro 32 (n = 14), GE Revolution EVO (n = 23), and Toshiba Aquilion (n = 161). All scans were obtained in the arterial phase, with slice thicknesses ranging from 0.6 to 5 mm, standardized to 3 mm in Vue Research PACS (Carestream Philips) using multiplanar reformatted images. Analysis was performed using Aquarius iNtuition Viewer (TeraRecon), following the same methodology as described by Röder et al.[22] A three-dimensional reconstruction was used to identify anatomical landmarks. The internal carotid artery was identified from clavicle to skull base. To distinguish calcified plaques from the contrast-enhanced lumen, patient-specific HU thresholds were applied, defined as the mean HU plus three standard deviations in a segment without calcifications. All voxels exceeding this threshold within the arterial segment were manually selected, and the calcium score was automatically calculated. All voxels exceeding this threshold within the arterial segment were manually selected, and the calcium score was automatically calculated. The calculation was performed over the entire contrast-enhanced area associated with each selected voxel, across all slices in which enhancement was visible. The software ensured that previously measured areas were not included again in subsequent slices, preventing duplication in the calcium score computation. The maximum HU value within each calcified lesion was recorded. A density weighting factor was subsequently assigned according to the standard Agatston method. The score for each lesion was calculated by multiplying the lesion area (in mm^2) by its respective density factor. The total carotid calcium score was then obtained by summing the individual lesion scores for each carotid artery. The calcium score was reported as a continuous, unitless numerical value.

Perivascular fat density surrounding the vessel, just beyond the adventitial layer, was measured following the method described by Baradaran et al.[21] The axial slice visually showing the largest calcifications was selected. Display settings were standardized (window width 500 HU, center 100 HU). Two manually placed circular regions of interest (ROIs) (each 2.5 mm in diameter) were positioned within the perivascular adipose tissue adjacent to the carotid artery on the side of the calcification, avoiding overlap and neighboring anatomical structures. The HU value of each pixel within the region of interest was measured, and the mean HU values were automatically calculated. Because the surface area of each ROI was standardized across measurements, it was not included in the score calculation. As a result, the average of the mean HU values from both ROIs was used for further analysis.

Statistical analysis. All statistical analyses were conducted using SPSS Statistics 28 software (IBM Corporation). A P value of $<.05$ was considered statistically significant. Descriptive statistics were used for all variables. The normality of continuous variables was assessed using histograms, skewness, and the Shapiro-Wilk test. Normally distributed data were expressed as mean ± standard deviation, whereas skewed distributed data were presented as median (IQR). For paired comparisons, the Wilcoxon signed-rank test was used for skewed data and the one-sample t test for normally distributed data. For unpaired comparisons, the Mann-Whitney U test was applied for two groups and the Kruskal-Wallis test for more than two groups (nonparametric), whereas the independent samples t test or analysis of variance was used for normally distributed variables. Measurement reliability was assessed using the intraclass correlation coefficient (ICC) from 10 randomly selected scans analyzed twice by the same observer and once by a second observer.

Associations between the calcium score and the presence of symptoms were assessed using the Mann-Whitney U test, whereas associations between fat density and symptomatology were analyzed using the independent samples t test. Logistic regression was used to assess the predictive value of the ipsilateral calcium score for early (<30 days) and late complications.

Unlike coronary calcium, carotid calcium risk group cutoffs are not yet validated. Therefore, the applied cutoff values serve as exploratory, population-specific tools for risk stratification in this cohort. Multiple potential cutoff values for calcium score and perivascular fat density risk groups were visually assessed using Kaplan-Meier survival curves and statistically compared using log-rank tests. The selected thresholds (800 for calcium score and −90 HU for perivascular fat density) corresponded to the values that showed the greatest separation in survival outcomes. Because of the skewed distribution of calcium scores, an additional high-risk category (>1600) was introduced, resulting in three groups: low (0-800), moderate (800-1600), and high risk (>1600). Subsequent analyses used risk groups; earlier analyses used the continuous variable.

Survival analysis was conducted using Kaplan-Meier curves to evaluate long-term outcomes, in relation to the ipsilateral carotid calcium score and ipsilateral perivascular fat density. The follow-up period for survival analysis was truncated at the point where fewer than 10% of patients remained at risk. This occurred after 7

years for neurological events, all-cause mortality, and cardiovascular death, and after 6 years for MACE and restenosis.

Cox proportional hazards models were used to assess the predictive value of the ipsilateral and contralateral calcium score, treating calcium score risk groups as an ordinal variable, and perivascular fat density for survival outcomes. Univariate Cox regression was conducted for known predictors of atherosclerosis progression, including age, sex, body mass index (BMI), smoking, DM, hypertension, dyslipidemia, and renal failure. Multivariate Cox regression was performed for ipsilateral calcium and perivascular fat density scores, including variables with $P < .10$ at univariate analysis, along with established strong clinical predictors from the literature (age, BMI, and DM), to adjust for potential confounders.

RESULTS

Demographics. A total of 358 scans were provided by the Hospital of Trieste to the University Medical Center Groningen. Of these scans, 197 were of sufficient quality to enable reliable measurements using the Aquarius iNtuition Viewer software. The Toshiba Aquilion scans were excluded from analysis because the slice spacing was too large and the in-plane pixel size too coarse, which compromised image resolution and rendered the scans incompatible with the image analysis software. Of the 197 eligible scans, 19 patients were excluded: 15 had previously undergone ipsilateral CEA, and 4 were duplicates. Consequently, 178 patients were included and their calcium scores and perivascular fat densities assessed. Baseline demographics are presented in Table I. The mean age was 74.1 years, with 62.9% male patients and 42.7% presenting symptomatically.

CT-scan analysis. Calcium scores were analyzed for both the ipsilateral (median: 478.0, IQR: 186.8-1500.5) and contralateral (median: 486.0, IQR: 176.0-1785.0) carotid artery, with no significant difference observed ($Z = -1.06$, $P = .29$). Calcium scores did not correlate with stenosis severity on duplex ultrasound examination, as determined by the NASCET[23] classification ($\rho = 0.089$, $P = .24$). The mean fat density was −88.7 (±16.6) HU on the ipsilateral side and −89.0 (±15.1) HU on the contralateral side, with no significant difference ($t = 0.30$, $P = .76$). Ipsilateral fat density did not differ significantly across stenosis severity groups ($F = 0.10$, $P = .96$) and showed no correlation with calcium score ($\rho = -0.058$, $P = .44$). Median calcium scores were comparable across all four CT scanners ($P = .50$), allowing combined analysis. Intraobserver variability showed moderate-to-good agreement (ICC = 0.72, $P = .004$), and interobserver variability was moderate (ICC = 0.51, $P = .036$). No learning effect was observed because of the researchers' prior experience.

Table I. Demographics of study population (N = 178)

Variable	Value
Age, years	74.1 (55-90) ± 7.4
Male sex	112 (62.9)
BMI	25.8 (17-36) ± 4.1
Right side of CEA	90 (50.6)
Symptomatology	
None	102 (57.3)
TIA (including amaurosis fugax)	39 (21.9)
Ischemic stroke	37 (20.8)
Days from symptom(s) to CEA	44.0 (20.0-97.0)
Smoking	
Nonsmoking	45 (25.3)
Past smoking	67 (37.6)
Active smoking	39 (21.9)
Unknown	27 (15.2)
Comorbidities	
Dyslipidemia	156 (87.6)
Diabetes mellitus	66 (37.1)
Hypertension	155 (87.1)
Cardiac history	
CAD	41 (23.0)
Previous PCI/CABG	23 (12.9)
CHF	16 (9.0)
Atrium fibrillation	20 (11.2)
COPD	23 (12.9)
History of cancer	26 (14.6)
CKD stage III-V (eGFR <60)	20 (11.2)
Medication	
Aspirin as only antiplatelet drug	113 (63.5)
Clopidogrel as only antiplatelet drug	13 (7.3)
Aspirin + clopidogrel	39 (21.9)

BMI, Body mass index; *CABG,* coronary artery bypass grafting; *CAD,* coronary artery disease; *CEA,* carotid endarterectomy; *CHF,* congestive heart failure; *CKD,* chronic kidney failure; *COPD,* chronic obstructive pulmonary disease; *eGFR,* estimated glomerular filtration rate; *PCI,* percutaneous intervention; *TIA,* transient ischemic attack.
Normally distributed continuous data are presented as mean (range) ± standard deviation, skewed distributed continuous data as median and (interquartile range), and categorical data as frequencies (percentage).

Symptoms and early complications. Neither the ipsilateral calcium score nor ipsilateral fat density was associated with preoperative symptoms ($P = .43$ and $P = .99$, respectively). None of the patients died within 30 days of surgery. Early postoperative complications (within 30 days) included cerebrovascular events (n = 9), cranial nerve palsy (n = 15), and postoperative bleeding (n = 14); no cases of myocardial infarction were reported. The ipsilateral calcium score was not significantly associated with individual early complications or their combined incidence (odds ratio: 1.23; $P = .20$). Similarly, perivascular

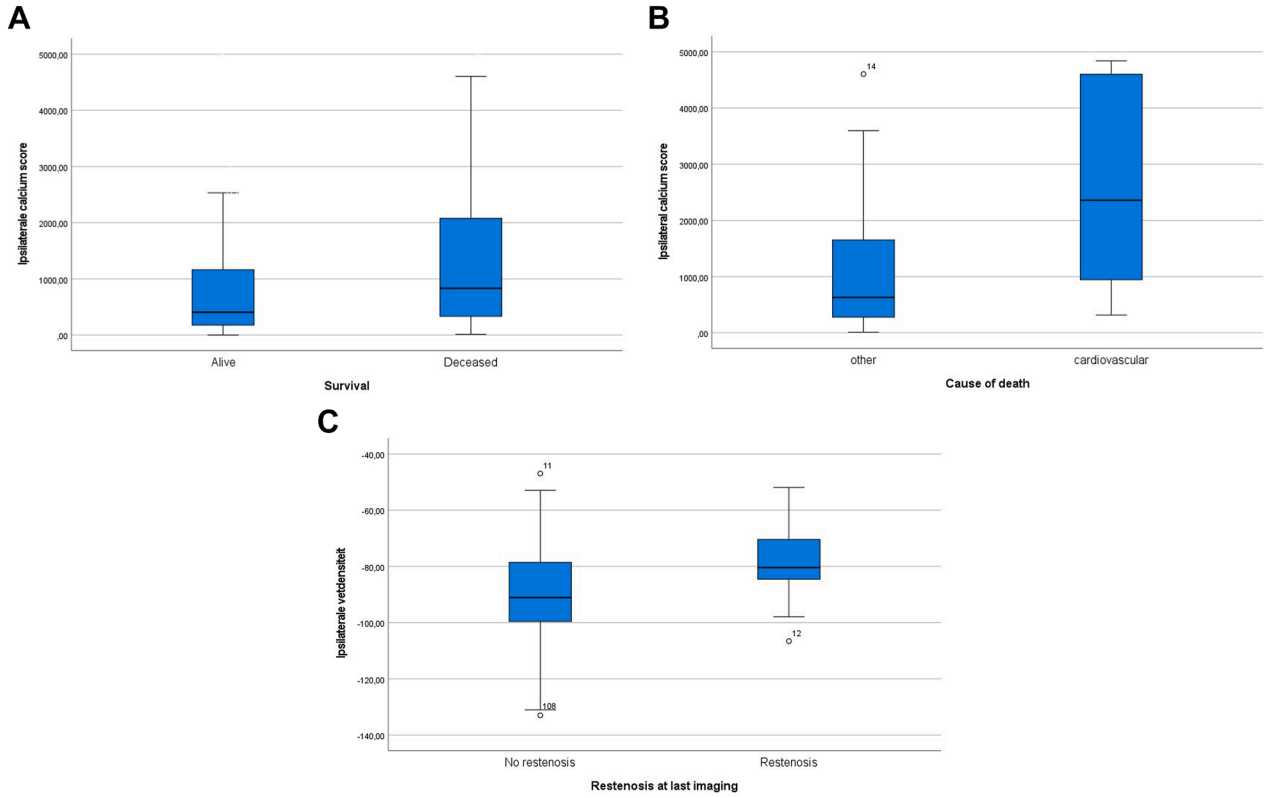

Fig 1. Distribution of carotid calcium scores and perivascular fat densities in different patient groups. **A,** Patients who died during follow-up had significantly higher calcium scores (835; interquartile range [IQR]: 317-2222) than those who survived (409; IQR: 117–1178) ($P = .045$). **B,** Patients who died of a cardiovascular cause during follow-up had higher calcium scores (2360; IQR: 789-4660) than those who died of other causes (631; IQR: 259-1662), however not statistically significant ($P = .054$). **C,** Patients with restenosis had higher perivascular fat density scores (−80.4 Hounsfield units [HU]; IQR: −87.9 HU to −69.8 HU) compared with those without restenosis (−91.1 HU; IQR: −99.8 HU to −78.6 HU), however not statistically significant ($P = .67$).

fat density did not predict early complications, individually or as a composite endpoint (odds ratio: 1.05; $P = .90$).

Long-term complications and mortality. Long-term complications included MACE (n = 45; 25.3%) and ipsilateral neurological events (n = 8; 4.5%). In 30 patients, the same event occurred twice, with the first instance recorded for analysis. It is worth noting that the rate of neurological events was higher in the symptomatic group (7.9%) compared with the asymptomatic group (2%). At the end of the study, 43 patients (24.2%) had died, with a mean survival of 41.6 ± 26.2 months. Causes of death included cardiovascular (n = 6), non-cardiovascular (n = 28), and unknown (n = 9). Median calcium scores were significantly higher in deceased patients (835; IQR: 317-2222) compared with survivors (409; IQR: 117-1178) ($P = .045$) (Fig 1, *A*). Among those who died, median calcium scores were higher in cardiovascular deaths (2360; IQR: 789-4660) than in non-cardiovascular deaths (631; IQR: 259-1662), although this difference was not statistically significant ($P = .054$) (Fig 1, *B*).

No significant difference in perivascular fat density was observed between patients who died and those who survived (mean −92.3 HU vs −87.6 HU; $P = .20$). However, patients who developed restenosis (n = 10; 5.6%) had higher median perivascular fat density values (−80.4 HU; IQR: −87.9 to −69.8) compared with those without restenosis (−91.1 HU; IQR: −99.8 to −78.6), though this difference did not reach statistical significance ($P = .67$) (Fig 1, *C*).

Survival analysis. Survival curves showed better outcomes in the low calcium group for MACE (74.9% vs 62.5%; $P = .041$), all-cause mortality (65.6% vs 58.1%; $P = .070$), and cardiovascular mortality (98.1% vs 91.5%; $P = .023$) at truncated follow-up (Fig 2, *A-C*). This association was not found for neurological events (Fig 2, *D*) and restenosis. The all-cause mortality curves diverged during the first 4 years of follow-up and then converged, suggesting differential risk early on. Therefore, survival differences were also assessed at 1 ($P = .34$), 2 ($P = .16$), 3 ($P = .071$), and 4 years ($P = .008$). At 4 years, overall survival was 60.7%, with 58.0% survival in patients with high

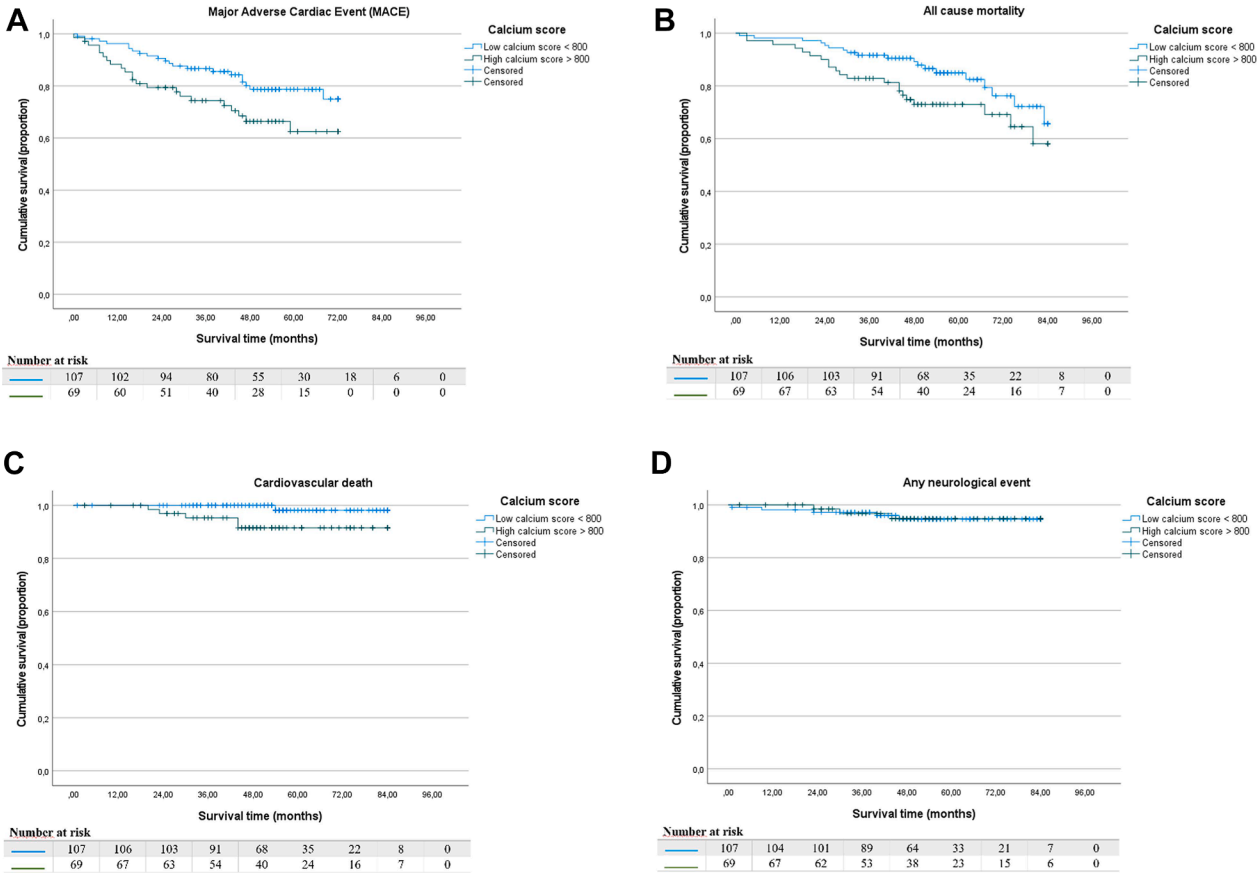

Fig 2. Kaplan-Meier survival curves comparing patients with high vs low calcium scores for four clinical outcomes: **(A)** major adverse cardiovascular events (*MACE*), **(B)** all-cause mortality, **(C)** cardiovascular mortality, and **(D)** any neurological event. Statistical differences between groups were assessed using the log-rank test. Significant differences were observed for MACE ($P = .041$) and cardiovascular mortality ($P = .023$), with a nonsignificant trend for all-cause mortality ($P = .070$). The number of patients at risk is shown below each graph, aligned with the corresponding time points.

calcium scores and 63.6% in those with low calcium scores ($P = .008$).

In asymptomatic patients, differences were even greater for MACE (79.3% vs 48.1%; $P = .005$) and all-cause mortality (78.2% vs 54.9%; $P = .004$). The number of cardiovascular deaths in this subgroup (n = 5) was too small for reliable analysis, and no significant association was found for neurological events. No significant survival differences were observed between high and low perivascular fat density groups for MACE, mortality, or neurological events. However, a substantial difference in survival curves for restenosis was observed between the groups after 6 years (95.5% vs 68.9%; Fig 3), with the difference approaching statistical significance ($P = .050$).

Predictors of outcome measures. Univariate Cox regression revealed that incremental increases in calcium score were significantly associated with MACE (hazard ratio [HR] = 1.50; 95% confidence interval [CI]: 1.07-2.09; $P = .018$) and cardiovascular death (HR = 3.20; 95% CI: 1.15-8.93; $P = .026$). A trend toward significance was seen for all-cause mortality (HR = 1.37; 95% CI: 0.98-1.93; $P = .07$). The risk of restenosis increased with an HR of 5.69 (95% CI: 1.18-27.4; $P = .030$) from low to high fat density scores. Additional variables associated with outcomes are presented in Table II. Univariate Cox regression was also repeated in the asymptomatic subgroup, showing stronger associations for MACE (HR = 1.99; 95% CI: 1.30-3.04; $P = .002$) and all-cause mortality (HR = 2.06; 95% CI: 1.22-3.45; $P = .006$). Additional results for this subgroup are presented in Table II.

Multivariate Cox regression confirmed the independent predictive value of the calcium score for MACE in the first model, with an HR of 1.63 (95% CI: 1.15-2.33; $P = .007$), and for cardiovascular death in the second model, with an HR of 3.12 (95% CI: 1.01-9.58; $P = .047$). The consistent trend observed for perivascular fat density in predicting restenosis, despite not reaching statistical

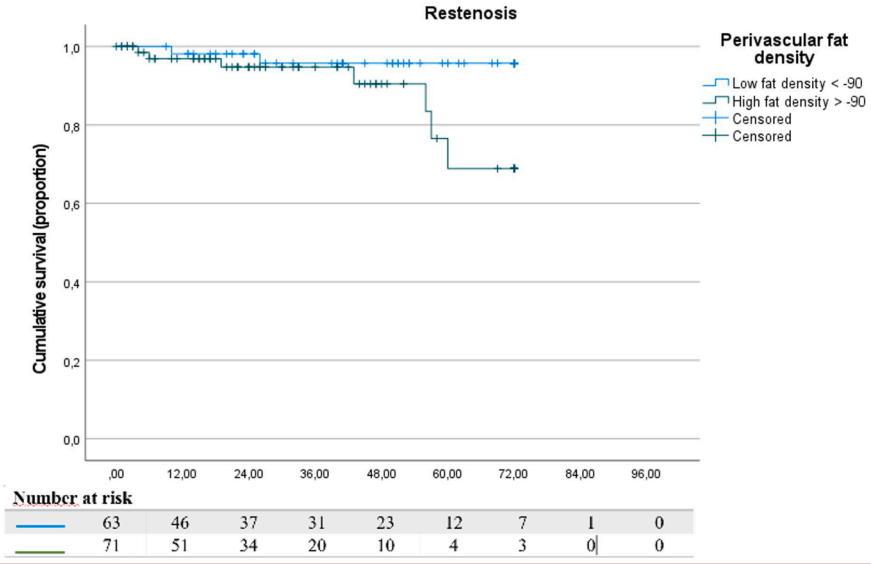

Fig 3. Kaplan-Meier survival curve comparing patients with high vs low perivascular fat density scores (in Hounsfield units) for the outcome of restenosis. A statistical difference between the groups was assessed using the log-rank test, showing a strong trend toward significance ($P = .050$). The number of patients at risk is displayed below the curve, aligned with the corresponding time points.

significance in the final model (HR = 5.51; 95% CI: 0.98-31.0; $P = .53$), underscores its potential clinical relevance and supports further investigation (Table III).

DISCUSSION

This retrospective study investigated whether ipsilateral carotid calcium score and perivascular fat density could serve as reliable predictors of complication risk after CEA, and whether they may assist in preoperative decision-making and individualized postoperative management. The current screening criterion, degree of stenosis, did not correlate with either calcium score or perivascular fat density. Notably, patients who died during follow-up had significantly higher calcium scores than survivors. Survival rates were significantly higher in asymptomatic patients with low calcium scores for MACE, all-cause mortality, and cardiovascular death, with the first and the latter reaching statistical significance in the entire research population over the full follow-up period as well. For perivascular fat density, a difference in HU was observed between patients with and without restenosis. This study confirmed the predictive value of the carotid calcium score for MACE and cardiovascular death, both across risk strata and after adjusting for confounders. It also identified perivascular fat density as a potential predictor of restenosis.

Currently, the degree of stenosis remains the primary criterion for selecting patients for CEA, according to the 2011 Society for Vascular Surgery guidelines.[24] Although this measure is strongly associated with procedural outcomes,[9] it is somewhat unexpected that no association was found between stenosis severity and the calcium score, especially given that the calcium score predicted several long-term outcomes. In 2006, Nandalur et al[25] suggested that carotid calcium scoring could be used as a marker of luminal stenosis, although subsequent studies failed to consistently validate this.[26] Moreover, degree of stenosis has been associated with symptomology and can predict complications and mortality after CEA, whereas the calcium score in this and other studies primarily predicted all-cause mortality.[5] This discrepancy may be explained by the fact that stenosis reflects the local disease burden, whereas calcium score reflects systemic atherosclerosis and overall cardiovascular health.[27] As such, both may be considered independent predictors of various clinical outcomes.

The role of calcium in plaque stability, and by extension, its association with symptomatology, remains controversial. Shi et al[28] reported that both the location (intimal vs medial) and morphology (size and shape) of calcification affect plaque behavior. Multiple small intimal calcifications are more likely to destabilize plaques, whereas larger, denser calcifications are associated with stability. These opposing effects could explain the inconsistent relationship between total calcium burden and plaque-related symptoms or cerebral ischemic events.[26] It is however interesting that total calcium burden was a stronger predictor of outcomes in asymptomatic patients. This may reflect that established calcification, detected by CT, is more indicative of chronic plaque stability and long-term risk rather than acute symptomatology, which is often driven by plaque instability, inflammation, or microcalcifications. These findings may guide clinical decision-making, especially in

Table II. Univariate Cox regression analysis of predictors and confounders for all-cause mortality after carotid endarterectomy

Outcome	Any neurological event		Major adverse cardiac event		All-cause mortality		Cardiovascular death		Restenosis	
Variable	HR	*P*	HR	*P*	HR	*P*	HR	*P*	HR	*P*
Age	1.07	.20	1.02	.42	**1.13**	**<.001**	1.15	.045	1.06	.25
Male sex	43.7	.21	1.54	.19	1.59	.19	1.24	.80	**0.23**	**.034**
BMI	1.02	.82	1.09	.060	0.94	.099	1.22	.63	0.97	.74
Smoking status	0.82	.72	1.18	.48	0.99	.98	1.11	.86	0.81	.65
Presence of symptoms	3.98	.091	0.67	.20	1.47	.22	0.24	.20	0.87	.84
Diabetes mellitus	2.42	.070	**1.56**	**.037**	1.00	.99	1.11	.86	0.67	.40
Hypertension	1.07	.95	0.87	.73	2.06	.23	0.77	.81	1.44	.73
Dyslipidemia	24.4	.51	1.12	.81	1.17	.76	24.0	.58	0.93	.93
Cardiac history	2.27	.25	**2.27**	**.006**	1.33	.39	4.60	.078	1.00	.99
COPD	0.04	.49	0.49	.23	1.35	.50	1.53	.70	1.02	.98
CKD stage III-V	**5.87**	**.016**	**2.41**	**.026**	**4.29**	**<.001**	2.13	.49	4.04	.11
eGFR	0.98	.17	0.99	.46	0.98	.021	0.99	.59	0.98	.34
Creatinine	2.22	.095	1.74	.069	1.64	.12	1.12	.91	2.39	.059
Hb	0.95	.77	0.93	.31	**0.89**	**.002**	0.76	.088	0.82	.14
LDL	1.00	.95	1.00	.88	0.99	.47	0.98	.070	1.00	.51
HDL	0.95	.16	0.99	.30	0.99	.53	0.95	.18	1.04	.16
Total cholesterol	0.99	.45	1.00	.97	1.00	.81	**0.97**	**.026**	1.00	.48
Triglycerides	0.99	.19	1.00	.72	1.00	.47	0.99	.22	1.00	.48
Amount of stenosis	0.89	.87	0.75	.33	1.03	.94	0.67	.57	2.57	.36
Ipsilateral calcium score	1.02	.97	**1.41**	**.041**	1.37	.069	**3.20**	**.026**	0.82	.63
	1.65	*.53*	***1.99***	***.002***	***2.06***	***.006***	*2.73*	*.065*	*0.72*	*.52*
Ipsilateral fat density	3.01	.18	1.09	.79	0.77	.42	2.08	.40	**5.69**	**.030**
	5.53	*.12*	*0.91*	*.80*	*0.57*	*.24*	*.42*	*.27*	*5.53*	*.12*

BMI, Body mass index; *COPD,* chronic obstructive pulmonary disease; *CKD,* chronic kidney disease; *eGFR,* estimated glomerular filtration rate; *Hb,* hemoglobin; *HR,* hazard ratio; *LDL/HDL,* low/high density lipoprotein.
Bold *P* values for statistical significance. Outcomes with $P < .05$ are indicated in bold. Outcomes in the asymptomatic patient group are shown in italics.

asymptomatic patients. Those with high calcium scores and limited life expectancy may benefit less from surgery, as the procedural risk is higher and event rate adjusted for survival time lower. These data may support more conservative management in this specific patient group. Alternative modalities, such as ^{18}F-sodium fluoride positron emission tomography imaging, may provide more biologically active markers of plaque instability, even before visible changes appear on CT.[29]

Higher perivascular fat density was linked to increased restenosis, though significance emerged only after longer follow-up. It is hypothesized that perivascular fat density reflects active inflammation and stenosis progression rather than a static disease marker. If confirmed in longitudinal studies, this marker could help identify patients who may benefit from intensified medical therapy peri- and postoperatively, potentially reducing the risk of reintervention.

For long-term complications, the calcium score was a significant predictor of both MACE and cardiovascular death. Carotid atherosclerosis is a recognized marker of systemic atherosclerosis and correlates with disease in other vascular beds, such as the coronary and iliac arteries.[30,31] Our findings align with prior studies: Baber et al[32] demonstrated that carotid atherosclerosis enhances cardiovascular risk prediction beyond traditional risk factors, and Sillesen et al[33] found carotid plaque burden to be a stronger predictor of coronary artery calcification than other peripheral vascular beds. These findings reinforce the role of carotid calcium scoring as a surrogate for systemic atherosclerosis. The carotid calcium score in our study was also associated with all-cause mortality, consistent with studies examining vascular calcification in the aorta, iliac, coronary, and carotid arteries.[22,34-36] Interestingly, its predictive value diminished after 5 years, likely reflecting the localized nature of CEA vs the systemic progression of atherosclerosis. Patients often present with overlapping risk factors from metabolic syndrome and cardiovascular disease, and all patients in this study had at least one

Table III. Multivariate Cox regression analysis of predictors for major adverse cardiac events (*MACE*), cardiovascular death, and restenosis after carotid endarterectomy

Variable	HR	95% CI lower	95% CI upper	*P*
Model 1 (MACE)				
Age	1.03	0.98	1.08	.22
BMI	1.06	0.98	1.15	.17
Diabetes mellitus	1.25	0.79	2.00	.34
Cardiac history	**2.21**	**1.14**	4.25	**.018**
CKD stage III-V	1.93	0.82	4.51	.13
Ipsilateral calcium score	**1.63**	**1.15**	**2.33**	**.007**
Model 2 (CV death)				
Age	**1.19**	**1.03**	**1.39**	**.023**
BMI	1.25	0.98	1.58	.073
Diabetes mellitus	0.73	0.15	3.51	.69
Total cholesterol	0.96	0.92	1.00	.052
Ipsilateral calcium score	**3.12**	**1.01**	**9.58**	**.047**
Model 3 (restenosis)				
Age	1.08	0.97	1.20	.18
BMI	1.06	0.87	1.29	.56
Diabetes mellitus	0.84	0.29	2.45	.74
Male sex	4.14	0.99	17.3	.052
Ipsilateral fat density	5.51	0.98	31.0	.053

BMI, Body mass index; *CI*, confidence interval; *CKD*, chronic kidney disease; *CV*, cardiovascular; *HR*, hazard ratio.
Bold *P* values for statistical significance. Outcomes with $P < .05$ are indicated in bold.

comorbidity.[37] The calcium score correlated most strongly with cardiovascular mortality, likely due to its focus on vascular health rather than comorbidities. Although Dudum et al[38] linked coronary calcification to cause-specific mortality, similar research on carotid calcium is scarce. By including perivascular fat density and assessing diverse outcomes, this study contributes to a more comprehensive understanding of carotid plaque characteristics. These two measures, calcium burden and fat density, are complementary but not interchangeable, reflecting different pathophysiological pathways. A more robust risk stratification model should integrate patient characteristics, timing and type of symptoms, and plaque features.[35] This study contributes specifically to that understanding by emphasizing the prognostic importance of plaque composition.

This study has several strengths. It validated the findings of a Dutch cohort in an independent Italian population using a standardized measurement protocol, thereby improving generalizability. Unlike prior studies that used calcium score intervals of 100 points, this study grouped patients into three broader categories, likely amplifying the observed mortality risk gradient. More detailed clinical data also allowed for better adjustment for confounders. Finally, the study addressed a clinically relevant question with multiple subanalyses. The lack of statistically significant associations for some outcomes may be due in part to the limited number of events, particularly for cardiovascular mortality and restenosis. Although trends were observed, the study may have been underpowered. In addition, heterogeneity in imaging protocols and follow-up duration, along with some subjectivity in image analysis (eg, manual ROI placement and slice selection), could have introduced measurement variability. Nevertheless, the overall methodology was standardized and reproducible, with moderate-to-good reliability scores. Unlike coronary artery calcium scoring, no universally accepted cutoff values exist for carotid calcium risk groups. Several studies[39-42] show that carotid calcium scores are generally higher than coronary scores due to differences in plaque surface area and artery anatomy, but no standard clinical thresholds have been established. Furthermore, contrast-enhanced CT affects attenuation values, complicating direct comparisons. Although validating a universal threshold is beyond this study's scope, our chosen 800 HU cutoff provides a meaningful risk distinction in our dataset and may aid future meta-analyses and validation efforts. Lastly, as the study only included patients with hemodynamically significant carotid stenosis scheduled for CEA, the findings may not apply to patients with mild stenosis or to high-risk patients unsuitable for surgery.

CONCLUSIONS

This single-center, observational retrospective cohort study confirmed the association between high ipsilateral carotid calcium score and the risk of MACE, cardiovascular death, and all-cause mortality, as well as a potential association between perivascular fat density and restenosis after CEA. The calcium score emerged as an independent risk factor for MACE and cardiovascular death, even after adjusting for age, BMI, DM, cardiac history, CKD stage III-V, and total cholesterol. This supports the value of calcium scoring as a marker of overall vascular health and a potential risk stratification tool in the preoperative assessment for CEA. This is particularly relevant in the asymptomatic patient group, were associations and predictive values were even stronger. Although perivascular fat density did not remain an independent predictor of restenosis in multivariable models, a trend was observed. Future research with larger sample sizes is needed to better define the role of perivascular fat and other plaque features in predicting long-term outcomes after CEA.

AUTHOR CONTRIBUTIONS

Conception and design: MK, MD, FR, RP, MU, JV, RS, CZ
Analysis and interpretation: MK, FR, RB, RS, CZ
Data collection: MK, MD, SL, RR
Writing the article: MK, RS, CZ
Critical revision of the article: MK, MD, FR, RB, RP, MU, SL, RR, JV, RS, CZ
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