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Basal Ganglia's Influence on Awake Testing in Carotid Endarterectomy

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Basal Ganglia's Influence on Awake Testing in Carotid Endarterectomy

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☒
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UC Dissertação - DECLARAÇÃO DE TRANSPARÊNCIA RELATIVAMENTE À UTILIZAÇÃO DE FERRAMENTAS DE CHATBOT GENERATIVO BASEADAS EM LARGE LANGUAGE MODELS

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☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

Faculdade de Medicina da Universidade do Porto, 07/10/2024

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Trabalho de acordo com as normas da revista "European Journal of Radiology"

Basal Ganglia's Influence on Awake Testing in Carotid Endarterectomy

Original research article

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Abstract:

Background

White matter changes (WMC) have been associated with the underlying presence of chronic cerebral ischemia, such as in carotid stenosis and age-related white matter changes (ARWMC). A low attenuation on computed tomography (CT) characterizes these alterations. Patients undergoing carotid endarterectomy (CEA) with severe WMC may be at increased risk of intraoperative neurologic deficits (IND) during carotid clamping. This study aims to determine the potential role of ARWMC as a predictor of IND during CEA with regional anesthesia (RA).

Methods

Patients undergoing CEA under RA at a tertiary referral center, who presented with IND during CEA were prospectively and consecutively recruited between January 2011 and December 2023. The control group comprised the immediately consecutive patient who underwent the same procedure without IND. From this sample, patients with preoperative CT were selected and compared based on ARWMC score ($\leq$ 1 and 2). Differences in demographics and comorbidities were assessed between the groups. A multivariable logistic regression was performed.

Results

One hundred and twenty-one patients were enrolled. Patients with IND had a significantly higher ARWMC score in basal ganglia (ARWMC-BG ≥ 2) and posterior circulation disease was more frequent (27.8%). No significant differences were observed in anatomical variations of the circle of Willis.

For patients with ARWMC-BG ≥ 2, a significant burden of other comorbidities was associated, such as chronic kidney disease, coronary disease, and atrial fibrillation. After multivariable logistic regression analysis, ARWMC-BG score ≥ 2 was an independent risk factor for IND (aOR 3.472).

Conclusion

An ARWMC-BG score above 2 predicts positive intraoperative “awake tests” in CEA with RA, constituting a reliable tool to stratify patients according to their risk of adverse events. However, larger prospective cohorts are needed to validate these findings and offer a better selection and management of this subset of patients.

Keywords:

carotid stenosis; brain ischemia; leukoaraiosis; regional anesthesia.

Glossary:

ARWMC – age-related white matter changes;

ARWMC-BG – age-related white matter changes in the basal ganglia;

CACC – carotid artery cross-clamping;

CBC – complete blood count;

CEA – carotid endarterectomy;

CKD – chronic kidney disease;

CS – carotid stenosis;

CT – computed tomography;

fPCA – fetal-type posterior cerebral arteries;

IND – intraoperative neurologic deficits;

MRI - magnetic resonance imaging;

SD – standard deviation;

RA – regional anesthesia.

Introduction

Carotid endarterectomy (CEA) is a surgical procedure in which the endothelium and atherosclerotic plaque are removed from the carotid wall. This procedure is indicated for moderate-to-severe asymptomatic or symptomatic carotid stenosis (CS) and is performed to reduce the risk of stroke (1). In patients with severe asymptomatic carotid stenosis who did not receive surgical treatment, the estimated incidence of carotid-related acute ischemic stroke is 4.7% over a five-year period (2). Additionally, among individuals aged 30-79 years, 21% have carotid plaque and 1.5% have CS (3).

Patients can be placed under local/regional (RA) or general anesthesia during CEA, since the anesthetic technique does not significantly affect clinically meaningful outcomes following CEA (4). Intraoperative neurologic deficits (IND), or a positive "awake test", is defined by clinical alterations in the neurologic examination during the procedure, once carotid clamping (CACC) occurs (5, 6). The gold-standard "awake test" is performed under RA and consists of an intraoperative neurological assessment resorting to a systematic timely clinical evaluation that includes time and place orientation checking, speech and mental capacity, motor activity, and level of consciousness (5, 7). Various factors have been associated with a positive awake test, such as contralateral carotid stenosis or occlusion (8, 9). It is worth noting that, during the procedure, there is a risk of CEA-related stroke, caused by cerebral embolism, thrombosis, or hypo-perfusion (10). Although 80 to 95 percent of patients tolerate CACC without intercurrences, alterations in the collateral circulation via the circle of Willis do not necessitate intraoperative carotid shunting (11).

Age-related white matter changes (ARWMC) can be identified in cerebral imaging by a high-intensity signal on T2-weighted magnetic resonance imaging (MRI) or a low attenuation on computed tomography (CT) in the periventricular/subcortical

white matter and deep gray matter (12, 13). It is believed to result from a combination of factors such as an enlargement of perivascular spaces, degeneration of myelinated axons, and disruption of the blood-brain barrier with subsequent leakage of fluid and inflammatory substances into the surrounding brain tissue (13-16). The development of white matter changes (WMC) is intimately related with cardiovascular risk factors such as dyslipidemia, diabetes mellitus, smoking, and particularly hypertension (17). The reason for this association is not yet defined; however, it is possibly due to the damage to the cerebral microcirculation (17, 18).

Clinically, ARWMC is associated with impairments in all dimensions of cognitive function, including general intelligence, attention and executive function, processing speed, and memory. (16, 19).

Considering the above rationale, patients with more severe WMC may be more susceptible to transient ischemic events during carotid clamping, possibly due to the conditioned cerebrovascular physiology. Specifically, ARWMC localized to the basal ganglia (ARWMC-BG) could reflect an increased vulnerability to ischemia, as this region is supplied by small penetrating arteries prone to ischemic changes. Despite these concerns, the potential role of ARWMC as a predictor of IND during CEA has not been fully explored.

Hence, the aim of the present study is to determine if ARWMC may serve as a potential predictor for a positive awake test during CEA under regional anesthesia. Identifying patients at higher risk, clinicians may be able to develop perioperative management strategies to improve outcomes and reduce adverse events.

Methods

Study Population

Between January 2012 and December 2023, patients undergoing CEA under RA at a tertiary referral center who presented with IND during the procedure were prospectively and consecutively selected. The controls consisted of the immediately consecutive patient who underwent the same intervention but did not develop IND, matched in a 1:1 ratio. Additionally, the center exclusion criteria for patients recruitment included synchronous cardiac surgery and patients *a priori* unwilling to stay awake during the procedure, resulting in the use of RA in 98% of cases(20). The present study was nested in this cohort, retrieving patients with a preoperative angio-CT. Patients without preoperative CT were excluded. Subsequently, patients were divided into two groups, based on their ARWMC scores: ARWMC ≤ 1 and ARWMC ≥ 2 (Figure 1 and 2).

Patients were evaluated before surgery by a vascular surgeon and an anesthesiologist. In cases of symptomatic stenosis, patients were also assessed by a neurologist. Participants were followed at 30, 90 days, and one year after discharge in the outpatient clinic, where they underwent clinical examination and Doppler ultrasound assessment. All patients were prescribed single antiplatelet (94 patients) or dual antiplatelet therapy (28 patients).

A preoperative CT scan was performed and evaluated within a maximum period of two months before the scheduled surgery. Radiological findings such as variations in the anterior and posterior circle of Willis (Figure 3), watershed stroke, fetal-type posterior cerebral arteries (fPCA), and posterior circulation disease were analyzed.

Blood samples were collected up to two weeks before surgery, and a complete blood count (CBC) was conducted using a Sysmex XE-2100 analyzer. Hematological

variables were quantified using the sodium lauryl sulfate method for hemoglobin or impedance and optical methods for the remaining parameters.

This study was reported according to the STrengthening the Reporting of OBservational studies in Epidemiology guidelines (STROBE) (21) and the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines (22). The local Ethics Committee approved the study protocol (number 248-18) and the European General Data Protection Act and Helsinki Declaration were adhered to. This study is registered on the ClinicalTrials.gov public website with the identifier NCT04347785.

Definitions

Neurologic deficits were defined as any persistent symptomatic alteration or sign during CACC neurologic examination (e.g., speech, motor function, and consciousness) after hemodynamic adjustment (23). The anesthesia-surgical team performed event notification.

CS was classified as symptomatic or asymptomatic following the clinical practice guidelines of the European Society of Vascular Surgery (24). CS assessment was conducted using either Doppler ultrasound based on velocimetric criteria or CT angiography using NASCET criteria (25).

ARWMC score was used for the assessment of WMC in CT images (26, 27). Non-contrast cranial CT is the imaging modality used to assess the ARWMC score, by evaluating the extent of white matter changes (12). WMC on CT scans were defined as ill-defined and moderately hypodense areas measuring ≥ 5mm. Lacunes were characterized as well-defined areas of >2mm <15mm with attenuation similar to cerebrospinal fluid. ARWMC in the basal ganglia (ARWMC-BG), which included the

striatum, globus pallidus, thalamus, internal and external capsules, and insula, were rated similarly and considered as white matter lesions, even if they were located <within gray matter nuclei containing a small amount of white matter. Ratings were conducted separately for the left and right hemispheres on a scale rating from 0 to 3 (12). A cutoff score of ARWMC $\leq$ 1 and ARWMC $\geq$ 2 was utilized, which has been previously described in the literature and based on the optimal binning statistical technique (28).

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

Surgical technique

More than 98% of CEA procedures are performed under RA in this referral center. The center has a reported stroke rate of 2% for CEA and a combined stroke/death rate of 2% (based on more than 100 procedures per year) (29). The exclusion criteria for RA include synchronous cardiac surgery and the patient's prior unwillingness to stay awake during the intervention.

Intraoperative monitoring consisted of consecutive brief awake neurological examinations and surveillance every 3 minutes during CACC. The neurological examinations were crucial in defining IND events (30).

Statistical Analysis

For statistical analysis, SPSS (IBM Corp., released 2023. IBM SPSS Statistics for Windows, version 29.0, Armonk, NY, USA) was used. Student’s t-test was favored for normally distributed continuous variables. Categorical data was presented as n (%) and continuous variables were presented as mean and standard deviation (SD) or median and range. The Mann-Whitney-U test was used for variables that did not assume

a normal distribution. The Chi-squared test was used to analyze categorical variables. Statistically significant results were set at a P-value < 0.05 level.

Multivariable logistic regression analysis was performed to determine independent clinical and demographic factors associated with IND. The predictive model was created using regression analysis and dimension reduction using the backward feature elimination method. Variables with clinical relevance included in the multivariable analysis were those associated with the IND group in the univariable analysis with statistical significance P < 0.2.

Results

A total of 121 patients were included in the study, with a mean age of 72.3 ± 8.3 years and 26 (21.5%) female patients (Table 1).

CKD was more prevalent in patients with ARWMC-BG ≥ 2 (36.4%) compared to those with ARWMC-BG ≤ 1 (17.2%) (P = 0.025). Similarly, coronary artery disease (CAD), was significantly higher in the ARWMC-BG ≥ 2 group (51.5% vs. 27.3%, P = 0.012). Additionally, atrial fibrillation (AF) was more common in the ARWMC-BG ≥ 2 group (15.2%) compared to the ARWMC-BG ≤ 1 group (4.6%) (P = 0.050) (Table 1). A sensitivity analysis was performed to evaluate the differences between the selected cohort and the patients without preoperative CT, and no differences were found.

Patients with IND presented significantly higher ARWMC scores in the basal ganglia (ARWMC-BG ≥ 2) compared to the control group (36.1% vs. 14.0%, P = 0.007) (Figure 3, Table 2). No significant differences between IND and control groups were found in the ARWMC in the cortex (44.4% vs. 34.0%, P = 0.247). Additionally, no significant differences were observed in anatomical variations of the circle of Willis between the groups with and without IND. Posterior circulation disease was more

prevalent in the IND group (27.8%) compared to controls (13.5%) (P = 0.014). No significant differences were observed for other variables (Table 2).

Multivariable logistic regression analysis identified ARWMC-BG ≥ 2 as a significant independent predictor for IND (aOR 3.472, 95% CI 1.367-8.821, P = 0.009). Other factors such as age, gender, BMI ≥30 kg/m2, ipsilateral stenosis, contralateral stenosis, ARWMC cortex ≥ 2, posterior circulation disease, and RDW-CV were included in the model. However, only ARWMC-BG ≥ 2 remained significant (Table 3).

Patients with a positive awake test and ARWMC >2 had a 30-day stroke risk of 9 (34.6%), which was not significantly higher than those with ARWMC >2 without neurological deficits (p=0.254). However, the presence of intraoperative neurological deficits (IND) proved to be a much better predictor of postoperative stroke (30 day), accounting for 85.7% (n=18) of all strokes in this cohort (P=0.006).

Discussion

This study demonstrated that patients with ARWMC-BG ≥ 2 were significantly more prone to experience IND during CEA compared to those with ARWMC-BG ≤ 1, with a three-fold higher risk of developing IND in patients with higher ARWMC-BG. At the cortex level, no relevant associations were found between the presence of ARWMC ≥2 and the occurrence of IND. Other significant findings included the higher prevalence of CKD, CAD, and AF in the patients with ARWMC ≥ 2, although these did not remain significant after multivariable analysis.

In fact, the observed data suggests that ARWMC in the basal ganglia can serve as a reliable predictor for the positive awake test during CEA. These findings are supported by previous research indicating that patients with small vessel disease, i.e. a

disorder of cerebral microvessels, are more likely to have WMC (31). Although the underlying pathologies behind WMC are heterogenous, histological studies propose that WMC is most likely a result of chronic hypoperfusion or ischemia leading to demyelination and, ultimately, axonal loss (15, 32). The basal ganglia are supplied by the lenticulostriate arteries (arterioles originating from the bilateral middle cerebral artery and anterior cerebral artery), and studies demonstrated that ARWMC-BG is most likely caused by mechanisms other than the anatomic narrowing of the penetrating arterioles lumen, such as hemodynamic abnormalities, impaired cerebral autoregulation, or a dysfunctional blood-brain barrier permeability (31, 33). This results in reduced cerebral blood flow reserve, increasing susceptibility to ischemia during the procedure when the carotid artery is clamped, and elevating the risk of IND (13, 34). Furthermore, severe degrees of ARWMC scores have been associated with significant cognitive burden, including a more than two-fold increased risk of ischemic stroke (35, 36). Even though CAD and Atrial fibrillation were not independent predictors, both are important cardiovascular risk factors believed to induce endothelial dysfunction, which has been supported in the progression of WMC network alterations (26, 27).

In contrast to the ARWMC-BG findings of this study, it was not found asignificant predictive value in anatomical variations of the circle of Willis for IND during CEA. This suggests that structural anomalies, while influential on overall cerebrovascular risk, do not provide the same level of predictive power for intraoperative events as the ARWMC scale (11). Although posterior circulation disease was more prevalent in the IND group, it remained insignificant in the multivariable analysis.

Additionally, this work did not find a predictive value for ARWMC in the cortex concerning IND during CEA. The basal ganglia are highly vascularized, with

penetrating arteries, making them particularly susceptible to ischemic changes and perfusion deficits, especially during CEA, when blood flow can be temporarily altered (37). Conversely, cortical regions, although also affected by chronic ischemic changes, have a more robust collateral circulation, which can potentially mitigate the impact of reduced perfusion during carotid clamping (38). Incorporating ARWMC-BG scores from preoperative CT into existing predictive models may improve the accuracy of anticipating a positive 'awake test' during CEA with RA, potentially enhancing perioperative decision-making and patient outcomes (39).

This work also reinforces the importance of brain CT scanning before CEA to identify patients at risk of postoperative neurologic complications, namely cerebral infarction and watershed strokes, and to exclude intracranial hemorrhage when peri-operative combination antiplatelet therapy is considered (40). This is in line with the current guidelines, which state that when a stenting procedure is considered, any duplex ultrasound should be followed by CT angiography or MR angiography, with the benefit of providing additional data on the aortic arch, as well as the extra- and intracranial circulation (24). Combination therapy with antiplatelets should be initiated after hemorrhage exclusion on imaging when symptomatic patients with 50-99% CS are selected for CEA (24). The authors also believe that performing a brain CT at the same time as the CT angiography would increase diagnostic accuracy in all patients proposed for CEA, as it is better to evaluate the brain parenchyma and the ARWMC.

However, this work was not exempted from limitations, as it was a study with a sample size of under 200 individuals, primarily male, and from a single tertiary referral center. Therefore, multicenter, and more extensive sample studies are necessary to confirm and validate the present results. Additionally, patients admitted to a tertiary referral center usually present with more significant comorbidities than those of

peripheral centers, which may introduce bias in interpreting results. Other limitation of this study is the lack of specific validation of MRI for predicting IND; further research is needed to explore MRI's role in this context, as our primary focus was to establish the predictive value of ARWMC identified through CT in assessing risk-benefit scenarios for surgical intervention. Differences among surgical teams were also not evaluated. A sensitivity analysis was performed to evaluate the differences between the selected cohort and the patients without preoperative CT, although subtle selection bias could not be excluded. Intraoperative hemodynamic parameters were unavailable, so a correlation with the present results could not be established.

Conclusion

An ARWMC-BG score ≥ 2 on preoperative CT scan is a potential predictor of a positive intraoperative “awake test” in CEA with RA. Furthermore, incorporating CT findings into existing predictive scores could enhance the accuracy in forecasting a positive 'awake test'. Further research is needed to explore MRI's role in this context, as the primary focus was to establish the predictive value of ARWMC identified through CT for assessing risk-benefit scenarios in surgical interventions. Identifying such predictors could help stratify patient risk and guide perioperative management strategies to optimize outcomes and minimize complications during carotid endarterectomy. Nonetheless, larger cohorts with consistent preoperative radiologic evaluation of these individuals are needed to validate these findings.

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Table 1 - Demographics, comorbidities and binary analysis

	ARWMC-BG≤ 1 N = 88	ARWMC-BG≥ 2 N= 33	P-value
Age (years) (mean ±SD)	72 ±8.2	73 ±8.5	0.622
Gender			
Male, n (%)	67 (76.1)	29 (87.9)	0.155
Female, n (%)	21 (23.9)	5 (12.1)	
Side (Right), n (%)	42 (51.9)	15 (45.5)	0.536
Cardiovascular risk factors			
Hypertension, n (%)	74 (84.1)	31 (93.9)	0.154
Diabetes, n (%)	43 (48.9)	12 (36.4)	0.219
Smoking history, n (%)	48 (54.5)	17 (51.5)	0.766
Dyslipidaemia, n (%)	75 (85.2)	29 (87.9)	0.709
BMI ≥30 kg /m^2, n (%)	9 (10.3)	6 (18.2)	0.246
CKD, n (%)	15 (17.2)	12 (36.4)	0.025
PAD, n (%)	19 (21.6)	8 (24.2)	0.755
CAD, n (%)	24 (27.3)	17 (51.5)	0.012
COPD, n (%)	17 (19.3)	4 (12.1)	0.523
CHF, n (%)	8 (9.3)	7 (21.2)	0.080
AF, n (%)	4 (4.6)	5 (15.2)	0.050

ASA, n (%) II III IV	 21 (23.9) 63 (71.6) 4 (4.5)	 5 (15.2) 26 (78.8) 2 (6.1)	0.569
Asymptomatic, n (%) Symptomatic, n (%) TIA Stroke	33 (41.8) 46 (58.2) 11 (13.9) 35 (44.3)	13 (39.4) 20 (60.6) 4 (12.1) 16 (48.5)	0.915
Stenosis Degree (mean ±SD) (%)	 83.3 ±11.4	 83.1± 10.3	0.943
Contralateral Stenosis Degree (mean ±SD) (%)	 61.8±1.82	 1.45±1.94	0.473
RDW-CV	13.38 (1.10)	13.80 (1.60)	0.188

Legend Table 1: ARWMC - BG – Age-related White Matter Changes in the basal Ganglia; 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 ≥ 1.5 mg/dl); COPD – Chronic obstructive pulmonary disease; IQR – Interquartile Range [25%-75%]; PAD – Peripheral artery disease; RDW-CV – Red Cell Distribution Width - Coefficient of Variation; SD – Standard Deviation.

Table 2 – Imagiologic markers distribution according to intraoperative neurologic deficits

	Control N =50	**IND N =72**	**p-value**
ARWMC Cortex ≥2, n (%)	17 (34.0)	32 (44.4)	0.247
ARWMC BG ≥2, n (%)	7 (14.0)	26 (36.1)	0.007
Circle of Willis – Anterior, n (%)	2 (6.0)	8 (17.8)	0.138
Circle of Willis – Posterior, n (%)	5 (15.6)	11 (24.4)	0.347
Watershed Stroke, n (%)	10 (45.5)	21 (51.2)	0.663
Fetal PCA, n (%)	6 (18.8)	11 (24.4)	0.553
Posterior Circulation Disease, n (%)	13 (13.5)	27 (27.8)	0.014
MCA stroke, n (%)	20 (76.9)	31 (77.5)	0.956
ACA stroke, n (%)	5 (19.2)	7 (17.5)	0.859
PCA stroke, n (%)	1 (4.8)	2 (6.3)	0.819

Legend Table 2: ACA stroke – Anterior Cerebral Artery related perioperative stroke; ARWMC Cortex – Age-related White Matter Changes in the cortex; ARWMC BG – Age-related White Matter Changes in the basal ganglia; Circle of Willis - Anterior – Hypoplastic or absent A1 segment of either of the anterior cerebral artery or anterior communicating ; Circle of Willis - Posterior – Hypoplastic or absent P1 segment of the ipsilateral posterior cerebral artery or posterior communicating artery; Fetal PCA – Fetal Posterior Cerebral Artery; IND – Intraoperative deficits during carotid clamping;

MCA stroke – Medium cerebral artery related perioperative stroke; PCA stroke – Posterior cerebral artery related perioperative stroke.

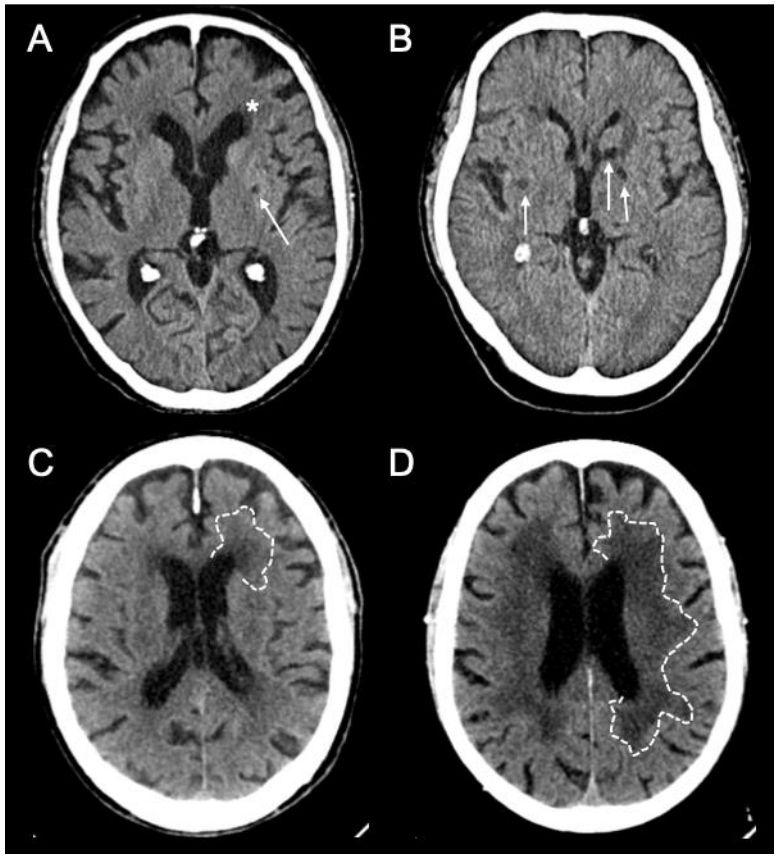
Table 3 – Multivariable analysis by resorting to a regressive predictive model.

	Intraoperative neurologic deficit			
	Crude OR (95%CI)	**P-value**	**aOR (95%CI)**	**P-value**
Age	1.025 (0.995-1.056)	0.102	NC	
Gender (female)	0.513 (0.27-0.972)	0.041	NC	
BMI >30 kg /m^2	1.010 (0.458-2.228)	0.980		
CAD	1.578 (0.722-3.447)	0.253		
CKD	2.457 (0.948-6.369)	0.064	NC	
Ipsilateral Stenosis	0.704 (0.538-0.923)	0.011	NC	
Contralateral Stenosis	1.251 (1.071-1.463)	0.005	NC	
ARWMC Cortex ≥2	1.553 (0.736-3.279)	0.248		
ARWMC Basal Ganglia ≥2	3.472 (1.367-8.821)	0.009	3.472 (1.367-8.821)	0.009
Posterior circulation Disease	2.463 (1.182-5.131)	0.016	NC	
RDW-CV	1.250 (1.002-1.561)	0.048	NC	

Legend Table 3: aOR - Adjusted odds ratio; BMI – Body Mass Index ARWMC - Age-related White Matter Changes; CAD – coronary artery disease; 95% CI - 95% confidence interval; CKD – Chronic kidney disease (creatinine ≥ 1.5 mg/dl); OR - Crude odds ratio; Posterior circulation disease – Stenosis >50% from either vertebral

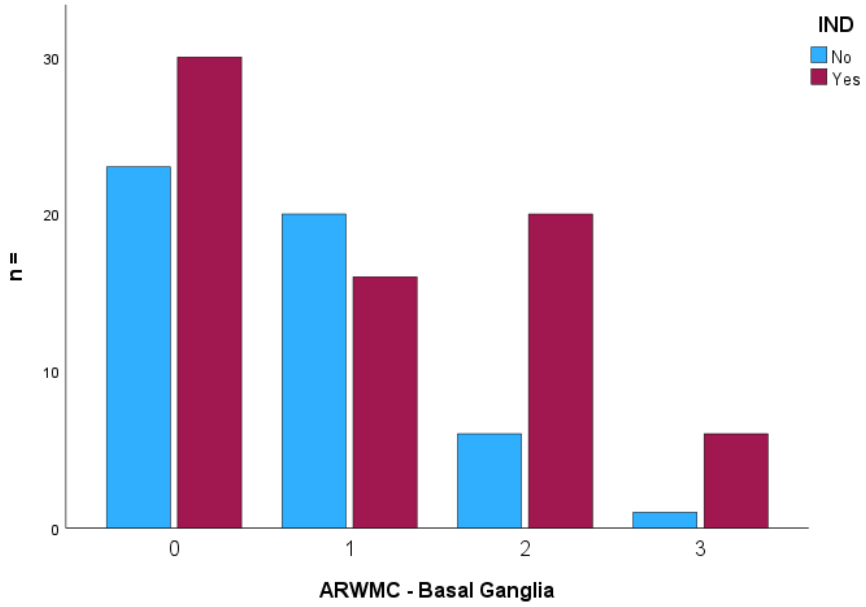
or basilar artery; RDW-CV – Red Cell Distribution Width - Coefficient of Variation; NC – Not Confirmed on multivariable analysis.

Figure 1 - White matter and basal ganglia hypodensities | examples of rating scores in axial CT scans

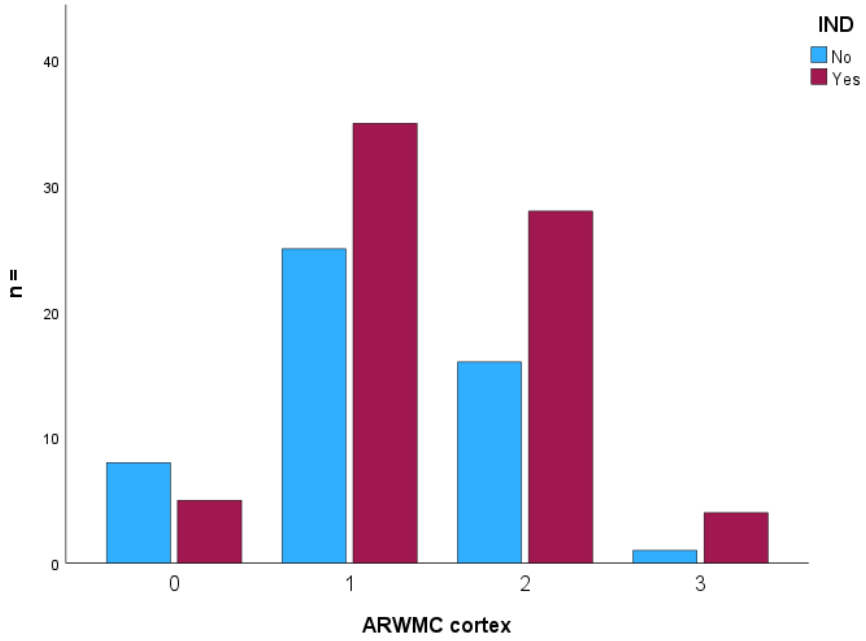


Legend Figure 1 – Patient 12 (A), with a rating score of ARWMC 1 (*) and ARWMC-BG of 1, depicting a single lenticular lacune (white arrow); Patient 8 (B) scored 2 on ARWMC-BG, with 3 non-confluent lesions (white arrows); Patient 3 (C) shows beginning of confluent periventricular white matter lesions (dotted line) – ARWMC score of 2; Patient 28 (D) showed diffuse and confluent of hemispheric white matter (dotted line), scoring 3 on the ARWMC.

Figure 2 - Distribution of Age-related white matter change

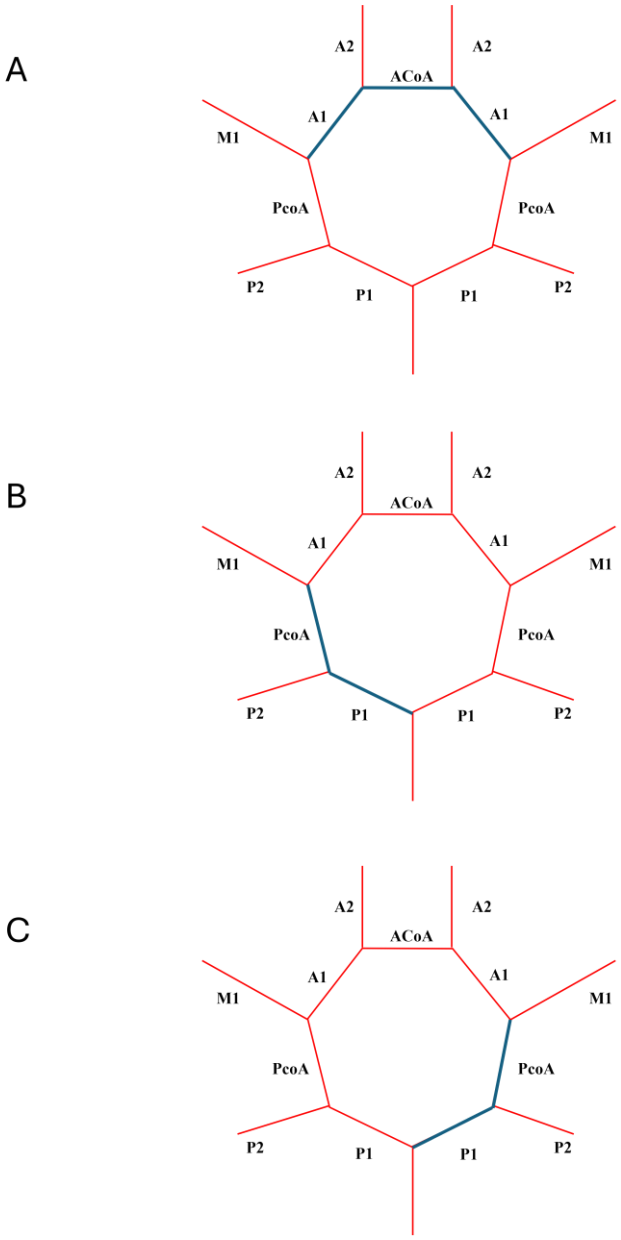


Legend Figure 2a - ARWMC - Age-related White Matter Changes – Basal Ganglia; IND - Intraoperative deficits during carotid clamping



Legend Figure 2b - ARWMC - Age-related White Matter Changes – Cortex; IND - Intraoperative deficits during carotid clamping

Figure 3 - Schematic Representation of the Circle of Willis Used for Patient Stratification



A - Circle of Willis - Anterior – Hypoplastic or absent A1 segment of either of the anterior cerebral artery or anterior communicating;

B - Right Side: Circle of Willis - Posterior – Hypoplastic or absent P1 segment of the ipsilateral posterior cerebral artery or posterior communicating artery;

C - Left Side: Circle of Willis - Posterior – Hypoplastic or absent P1 segment of the ipsilateral posterior cerebral artery or posterior communicating artery.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Página 7: "Original research article"
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Página 9: "This study aims to determine the potential role of ARWMC as a predictor of IND during CEA with regional anesthesia (RA)."; "Patients undergoing CEA under RA at a tertiary referral center who presented with IND during CEA were prospectively and consecutively recruited between January 2011 and December 2023."; "An ARWMC-BG score above 2 predicts positive intraoperative "awake tests" in CEA with RA, constituting a reliable tool to stratify patients according to their risk of adverse events."
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Página 13: "Considering the above rationale, patients with more severe WMC may be more susceptible to transient ischemic events during carotid clamping, possibly due to the conditioned cerebrovascular physiology. Specifically, ARWMC localized to the basal ganglia (ARWMC-BG) could reflect an increased vulnerability to ischemia, as this region is supplied by small penetrating arteries prone to ischemic changes. Despite these concerns, the potential role of ARWMC as a predictor of IND during CEA has not been fully explored."
Objectives	3	State specific objectives, including any prespecified hypotheses	Página 13: "…the aim of the present study is to determine if ARWMC may serve as a potential predictor for a positive awake test during CEA under regional anesthesia."
Methods			
Study design	4	Present key elements of study design early in the paper	Página 14: "Patients undergoing CEA under RA at a tertiary referral center who presented with IND during the procedure were prospectively and consecutively selected. The controls consisted of the immediately consecutive patient who underwent the same intervention but did not develop IND, matched in a 1:1 ratio."
Setting	5	Describe the setting, locations, and relevant dates, including	Página 14: "Between January 2012 and December 2023, patients undergoing CEA under RA at a tertiary referral center who presented

		periods of recruitment, exposure, follow-up, and data collection	with IND during the procedure were prospectively and consecutively selected"; "Participants were followed at 30, 90 days, and one year after discharge in the outpatient clinic where they underwent clinical examination and Doppler ultrasound assessment."
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Página 14: "Between January 2012 and December 2023, patients undergoing CEA under RA at a tertiary referral center who presented with IND during the procedure were prospectively and consecutively selected."; "…the center exclusion criteria for patients recruitment included synchronous cardiac surgery and patients a priori unwilling to stay awake during the procedure resulting in the use of RA in 98% of cases."; "Patients without preoperative CT were excluded."; " Participants were followed at 30, 90 days, and one year after discharge in the outpatient clinic, where they underwent clinical examination and Doppler ultrasound assessment."
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Página 14: "The controls consisted of the immediately consecutive patient who underwent the same intervention but did not develop IND matched in a 1:1 ratio."
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Página 15: "Neurologic deficits were defined as any persistent symptomatic alteration or sign during CACC neurologic examination (e.g., speech, motor function, and consciousness) after hemodynamic adjustment"; "Age-related white matter changes (ARWMC) score was used for the assessment of WMC in CT images."
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Página 12:"The gold-standard 'awake test' is performed under RA and consists of an intraoperative neurological assessment resorting to a systematic timely clinical evaluation that includes time and place orientation, checking speech and mental capacity, motor activity, and level of consciousness." Página 14: "A preoperative CT scan was performed and evaluated within a maximum period of two months before the scheduled surgery. Radiological findings such as variations in the anterior and posterior circle of Willis,

			watershed stroke, fetal-type posterior cerebral arteries (fPCA), and posterior circulation disease were analyzed"; Página 15: "ARWMC score was used for the assessment of WMC in CT images. Non-contrast cranial CT is the imaging modality used to assess the ARWMC score, by evaluating the extent of white matter changes. WMC on CT scans were defined as ill-defined and moderately hypodense areas measuring ≥ 5mm. Lacunes were characterized as well-defined areas of >2mm <15mm with attenuation similar to cerebrospinal fluid. ARWMC in the basal ganglia (ARWMC-BG), which included the striatum, globus pallidus, thalamus, internal and external capsules, and insula, were rated similarly and considered as white matter lesions, even if they were located <within gray matter nuclei containing a small amount of white matter. Ratings were conducted separately for the left and right hemispheres on a scale rating from 0 to 3. A cutoff score of ARWMC ≤ 1 and ARWMC ≥ 2 was utilized, which has been previously described in the literature and based on the optimal binning statistical technique."; "Neurologic deficits were defined as any persistent symptomatic alteration or sign during CACC neurologic examination (e.g., speech motor function and consciousness) after hemodynamic adjustment."
Bias	9	Describe any efforts to address potential sources of bias	Página 17: "A sensitivity analysis was performed to evaluate the differences between the selected cohort and the patients without preoperative CT and no differences were found."
"Study size	10	Explain how the study size was arrived at	Página 17: "A total of 121 patients were included in the study with a mean age of 72.3 ± 8.3 years and 26 (21.5%) female patients."
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Página 14: "…patients were divided into two groups based on their ARWMC scores: ARWMC ≤ 1 and ARWMC ≥ 2."; Página 16: " Statistical analysis included Student's t-test for normally distributed continuous variables."
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Página 16: "Student's t-test was favored for normally distributed continuous variables. Categorical data was presented as n (%) and continuous variables were presented as mean

			and standard deviation (SD) or median and range. The Mann-Whitney-U test was used for variables that did not assume a normal distribution. The Chi-squared test was used to analyze categorical variables. Statistically significant results were set at a P-value < 0.05 level. Multivariable logistic regression analysis was performed to determine independent clinical and demographic factors associated with IND. The predictive model was created using regression analysis and dimension reduction using the backward feature elimination method."
		(*b*) Describe any methods used to examine subgroups and interactions	Página 16: "The predictive model was created using regression analysis and dimension reduction using the backward feature elimination method. Variables with clinical relevance included in the multivariable analysis were those associated with the IND group in the univariable analysis with statistical significance P < 0.2."
		(*c*) Explain how missing data were addressed	Página 17: "A sensitivity analysis was performed to evaluate the differences between the selected cohort and the patients without preoperative CT, and no differences were found."
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Página 14: "Participants were followed at 30, 90 days, and one year after discharge in the outpatient clinic, where they underwent clinical examination and Doppler ultrasound assessment."
		(*e*) Describe any sensitivity analyses	Página 17: "A sensitivity analysis was performed to evaluate the differences between the selected cohort and the patients without preoperative CT and no differences were found"
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included	Página 14: "Between January 2012 and December 2023, patients undergoing CEA under RA at a tertiary referral center who presented with IND during the procedure were prospectively and consecutively selected. The

		in the study, completing follow-up, and analysed	controls consisted of the immediately consecutive patient who underwent the same intervention but did not develop IND, matched in a 1:1 ratio."; Página 17: "A total of 121 patients were included in the study, with a mean age of 72.3 ± 8.3 years and 26 (21.5%) female patients (Table 1)."
		(b) Give reasons for non-participation at each stage	Página 14: "Additionally, the center exclusion criteria for patients recruitment included synchronous cardiac surgery and patients a priori unwilling to stay awake during the procedure, resulting in the use of RA in 98% of cases."
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Página 17: "A total of 121 patients were included in the study, with a mean age of 72.3 ± 8.3 years and 26 (21.5%) female patients. CKD was more prevalent in patients with ARWMC-BG ≥ 2 (36.4%) compared to those with ARWMC-BG ≤ 1 (17.2%) (P = 0.025). Similarly, coronary artery disease (CAD), was significantly higher in the ARWMC-BG ≥ 2 group (51.5% vs. 27.3%, P = 0.012). Additionally, atrial fibrillation (AF) was more common in the ARWMC-BG ≥ 2 group (15.2%) compared to the ARWMC-BG ≤ 1 group (4.6%) (P = 0.050)."
		(b) Indicate number of participants with missing data for each variable of interest	Sem participantes com informações em falta.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Página 14: "Participants were followed at 30, 90 days, and one year after discharge in the outpatient clinic, where they underwent clinical examination and Doppler ultrasound assessment."
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time *Case-control study*—Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study*—Report numbers of outcome events or summary measures	Página 17: "A total of 121 patients were included in the study, with a mean age of 72.3 ± 8.3 years and 26 (21.5%) female patients (Table 1)."; "Patients with IND presented significantly higher ARWMC scores in the basal ganglia (ARWMC-BG ≥ 2) compared to the control group (36.1% vs. 14.0%, P = 0.007) (Figure 3, Table 2).
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which	Página 18: "Multivariable logistic regression analysis identified ARWMC-BG ≥ 2 as a significant independent predictor for IND (aOR 3.472, 95% CI 1.367-8.821; P = 0.009). Other factors such as age, gender, BMI ≥30 kg/m2,

		confounders were adjusted for and why they were included	ipsilateral stenosis, contralateral stenosis, ARWMC cortex ≥ 2, posterior circulation disease, and RDW-CV were included in the model."
		(*b*) Report category boundaries when continuous variables were categorized	Página 16: "A cutoff score of ARWMC ≤ 1 and ARWMC ≥ 2 was utilized, which has been previously described in the literature and based on the optimal binning statistical technique."
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Página 17: "A sensitivity analysis was performed to evaluate the differences between the selected cohort and the patients without preoperative CT and no differences were found."
Discussion			
Key results	18	Summarise key results with reference to study objectives	Página 18: "In fact, the observed data suggests that ARWMC in the basal ganglia can serve as a reliable predictor for the positive awake test during CEA. These findings are supported by previous research indicating that patients with small vessel disease, i.e. a disorder of cerebral microvessels, are more likely to have WMC."
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Página 20: "However, this work was not exempted from limitations, as it was a study with a sample size of under 200 individuals, primarily male, and from a single tertiary referral center. Therefore, multicenter, and more extensive sample studies are necessary to confirm and validate the present results. Additionally, patients admitted to a tertiary referral center usually present with more significant comorbidities than those of peripheral centers, which may introduce bias in interpreting results. Other limitation of this study is the lack of specific validation of MRI for predicting IND; further research is needed to explore MRI's role in this context, as our primary focus was to establish the predictive value of ARWMC identified through CT in assessing risk-benefit scenarios for surgical intervention. Differences among surgical teams were also not evaluated. A sensitivity analysis was performed to evaluate the differences between the selected cohort and the patients without preoperative CT, although subtle selection bias could not be excluded.

			Intraoperative hemodynamic parameters were unavailable, so a correlation with the present results could not be established."
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Página 20: "Therefore, multicenter, and more extensive sample studies are necessary to confirm and validate the present results." Página 21: "Identifying such predictors could help stratify patient risk and guide perioperative management strategies to optimize outcomes and minimize complications during carotid endarterectomy. Nonetheless, larger cohorts with consistent preoperative radiologic evaluation of these individuals are needed to validate these findings."
Generalisability	21	Discuss the generalisability (external validity) of the study results	Página 20: "However, this work was not exempted from limitations, as it was a study with a sample size of under 200 individuals, primarily male, and from a single tertiary referral center. Therefore, multicenter, and more extensive sample studies are necessary to confirm and validate the present results."
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Página 9: "This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors."

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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- Affiliations. Add affiliation addresses, referring to where the work was carried out, below the author names. Indicate affiliations using a lower-case superscript letter immediately after the author's name and in front of the corresponding address. Ensure that you provide the full postal address of each affiliation, including the country name and, if available, the email address of each author.
- Corresponding author. Clearly indicate who will handle correspondence for your article at all stages of the refereeing and publication process and also post-publication. This responsibility includes answering any future queries about your results, data, methodology and materials. It is important that the email address and contact details of your corresponding author are kept up to date during the submission and publication process.
- Present/permanent address. If an author has moved since the work described in your article was carried out, or the author was visiting during that time, a "present address" (or "permanent address") can be indicated by a footnote to the author's name. The address where the author carried out the work must be retained as their main affiliation address. Use superscript Arabic numerals for such footnotes.

Abstract

You are required to provide a concise and factual abstract which does not exceed 250 words. The abstract should briefly state the purpose of your research, principal results and major conclusions. Some guidelines:

- Abstracts must be able to stand alone as abstracts are often presented separately from the article.
- Avoid references. If any are essential to include, ensure that you cite the author(s) and year(s).
- Avoid non-standard or uncommon abbreviations. If any are essential to include, ensure they are defined within your abstract at first mention.

Keywords

You are required to provide 1 to 7 keywords for indexing purposes. Keywords should be written in English. Please try to avoid keywords consisting of multiple words (using "and" or "of").

We recommend that you only use abbreviations in keywords if they are firmly established in the field.

Highlights

You are required to provide article highlights at submission.

Highlights are a short collection of bullet points that should capture the novel results of your research as well as any new methods used during your study. Highlights will help increase the discoverability of your article via search engines. Some guidelines:

- Submit highlights as a separate editable file in the online submission system with the word "highlights" included in the file name.
- Highlights should consist of 3 to 5 bullet points, each a maximum of 85 characters, including spaces.

We encourage you to view example article highlights and read about the benefits of their inclusion.

Graphical abstract

You are encouraged to provide a graphical abstract at submission.

The graphical abstract should summarize the contents of your article in a concise, pictorial form which is designed to capture the attention of a wide readership. A graphical abstract will help draw more attention to your online article and support readers in digesting your research. Some guidelines:

- Submit your graphical abstract as a separate file in the online submission system.
- Ensure the image is a minimum of 531 x 1328 pixels (h x w) or proportionally more and is readable at a size of 5 x 13 cm using a regular screen resolution of 96 dpi.
- Our preferred file types for graphical abstracts are TIFF, EPS, PDF or MS Office files.

We encourage you to view example graphical abstracts and read about the benefits of including them.

Units, classifications codes and nomenclature

This journal requires you to use the international system of units (SI) which follows internationally accepted rules and conventions. If other units are mentioned within your article, you should provide the equivalent unit in SI.

Tables

Tables must be submitted as editable text, not as images. Some guidelines:

- Place tables next to the relevant text or on a separate page(s) at the end of your article.
- Cite all tables in the manuscript text.
- Number tables consecutively according to their appearance in the text.
- Please provide captions along with the tables.
- Place any table notes below the table body.
- Avoid vertical rules and shading within table cells.

We recommend that you use tables sparingly, ensuring that any data presented in tables is not duplicating results described elsewhere in the article.

Figures, images and artwork

Figures, images, artwork, diagrams and other graphical media must be supplied as separate files along with the manuscript. We recommend that you read our detailed artwork and media instructions. Some excerpts:

When submitting artwork:

- Cite all images in the manuscript text.
- Number images according to the sequence they appear within your article.
- Submit each image as a separate file using a logical naming convention for your files (for example, Figure_1, Figure_2 etc).
- Please provide captions along with the artwork.
- Text graphics may be embedded in the text at the appropriate position. If you are working with LaTeX, text graphics may also be embedded in the file.

Artwork formats

When your artwork is finalized, "save as" or convert your electronic artwork to the formats listed below taking into account the given resolution requirements for line drawings, halftones, and line/halftone combinations:

- Vector drawings: Save as EPS or PDF files embedding the font or saving the text as "graphics."
- Color or grayscale photographs (halftones): Save as TIFF, JPG or PNG files using a minimum of 300 dpi (for single column: min. 1063 pixels, full page width: 2244 pixels).
- Bitmapped line drawings: Save as TIFF, JPG or PNG files using a minimum of 1000 dpi (for single column: min. 3543 pixels, full page width: 7480 pixels).
- Combinations bitmapped line/halftones (color or grayscale): Save as TIFF, JPG or PNG files using a minimum of 500 dpi (for single column: min. 1772 pixels, full page width: 3740 pixels).

Please do not submit:

- files that are too low in resolution (for example, files optimized for screen use such as GIF, BMP, PICT or WPG files).
- disproportionally large images compared to font size, as text may become unreadable.

Figure captions

All images must have a caption. A caption should consist of a brief title (not displayed on the figure itself) and a description of the image. We advise you to keep the amount of text in any image to a minimum, though any symbols and abbreviations used should be explained.

Provide captions in a separate file.

Color artwork

If you submit usable color figures with your accepted article, we will ensure that they appear in color online.

Please ensure that color images are accessible to all, including those with impaired color vision. Learn more about color and web accessibility.

For articles appearing in print, you will be sent information on costs to reproduce color in the printed version, after your accepted article has been sent to production. At this stage, please indicate if your preference is to have color only in the online version of your article or also in the printed version.

Generative AI and Figures, images and artwork

Please read our policy on the use of generative AI and AI-assisted tools in figures, images and artwork, which states:

- We do not permit the use of Generative AI or AI-assisted tools to create or alter images in submitted manuscripts.
- The only exception is if the use of AI or AI-assisted tools is part of the research design or methods (for example, in the field of biomedical imaging). If this is the case, such use must be described in a reproducible manner in the methods section, including the name of the model or tool, version and extension numbers, and manufacturer.
- The use of generative AI or AI-assisted tools in the production of artwork such as for graphical abstracts is not permitted. The use of generative AI in the production of cover art may in some cases be allowed, if the author obtains prior permission from the journal editor and publisher, can demonstrate that all necessary rights have been cleared for the use of the relevant material, and ensures that there is correct content attribution.

Supplementary material

We encourage the use of supplementary materials such as applications, images and sound clips to enhance research. Some guidelines:

- Cite all supplementary files in the manuscript text.
- Submit supplementary materials at the same time as your article. Be aware that all supplementary materials provided will appear online in the exact same file type as received. These files will not be formatted or typeset by the production team.
- Include a concise, descriptive caption for each supplementary file describing its content.
- Provide updated files if at any stage of the publication process you wish to make changes to submitted supplementary materials.
- Do not make annotations or corrections to a previous version of a supplementary file.
- Switch off the option to track changes in Microsoft Office files. If tracked changes are left on, they will appear in your published version.

We recommend you upload research data to a suitable specialist or generalist repository. Please read our guidelines on sharing research data for more information on depositing, sharing and using research data and other relevant research materials.

Video

This journal accepts video material and animation sequences to support and enhance your scientific research. We encourage you to include links to video or animation files within articles. Some guidelines:

- When including video or animation file links within your article, refer to the video or animation content by adding a note in your text where the file should be placed.
- Clearly label files ensuring the given file name is directly related to the file content.
- Provide files in one of our recommended file formats. Files should be within our preferred maximum file size of 150 MB per file, 1 GB in total.
- Provide "stills" for each of your files. These will be used as standard icons to personalize the link to your video data. You can choose any frame from your video or animation or make a separate image.
- Provide text (for both the electronic and the print version) to be placed in the portions of your article that refer to the video content. This is essential text, as video and animation files cannot be embedded in the print version of the journal.

We publish all video and animation files supplied in the electronic version of your article.

For more detailed instructions, we recommend that you read our guidelines on submitting video content to be included in the body of an article.

Research data

We are committed to supporting the storage of, access to and discovery of research data, and our research data policy sets out the principles guiding how we work with the research community to support a more efficient and transparent research process.

Research data refers to the results of observations or experimentation that validate research findings, which may also include software, code, models, algorithms, protocols, methods and other useful materials related to the project.

Please read our guidelines on sharing research data for more information on depositing, sharing and using research data and other relevant research materials.

For this journal, the following instructions from our research data guidelines apply.

Option B: Research data deposit, citation and linking

You are **encouraged** to:

- Deposit your research data in a relevant data repository.
- Cite and link to this dataset in your article.
- If this is not possible, make a statement explaining why research data cannot be shared.

Data statement

To foster transparency, you are encouraged to state the availability of any data at submission.

Ensuring data is available may be a requirement of your funding body or institution. If your data is unavailable to access or unsuitable to post, you can state the reason why (e.g., your research data includes sensitive or confidential information such as patient data) during the submission process. This statement will appear with your published article on ScienceDirect.

Read more about the importance and benefits of providing a data statement.

Data linking

Linking to the data underlying your work increases your exposure and may lead to new collaborations. It also provides readers with a better understanding of the described research.

If your research data has been made available in a data repository there are a number of ways your article can be linked directly to the dataset:

- Provide a link to your dataset when prompted during the online submission process.
- For some data repositories, a repository banner will automatically appear next to your published article on ScienceDirect.
- You can also link relevant data or entities within the text of your article through the use of identifiers. Use the following format: Database: 12345 (e.g. TAIR: AT1G01020; CCDC: 734053; PDB: 1XFN).

Learn more about linking research data and research articles in ScienceDirect.

Research Elements

This journal enables the publication of research objects (e.g. data, methods, protocols, software and hardware) related to original research in Elsevier's Research Elements journals.

Research Elements are peer-reviewed, open access journals which make research objects findable, accessible and reusable. By providing detailed descriptions of objects and their application with links to the original research article, your research objects can be placed into context within your article.

You will be alerted during submission to the opportunity to submit a manuscript to one of the Research Elements journals. Your Research Elements article can be prepared by you, or by one of your collaborators.

Article structure

Article sections

Divide your manuscript into clearly defined sections covering all essential elements. For example:

- Abstract

- Keywords
- Introduction
- Materials and methods
- Results
- Conclusions
- Artwork
- Tables with captions

Introduction

The introduction should clearly state the objectives of your work. We recommend that you provide an adequate background to your work but avoid writing a detailed literature overview or summary of your results.

Methods

The methods section should provide sufficient details about your materials and methods to allow your work to be reproduced by an independent researcher. Some guidelines:

- If the method you used has already been published, provide a summary and reference the originally published method.
- If you are quoting directly from a previously published method, use quotation marks and cite the source.
- Describe any modifications that you have made to existing methods.

Results

Results should be clear and concise. We advise you to read the sections in this guide on supplying tables, artwork, supplementary material and sharing research data.

Discussion

The discussion section should explore the significance of your results but not repeat them. You may combine your results and discussion sections into one section, if appropriate. We recommend that you avoid the use of extensive citations and discussion of published literature in the discussion section.

Conclusion

The conclusion section should present the main conclusions of your study. You may have a stand-alone conclusions section or include your conclusions in a subsection of your discussion or results and discussion section.

Glossary

Please provide definitions of field-specific terms used in your article, in a separate list.

Abbreviations

Abbreviations which are not standard in the field should be defined in a footnote on the first page of your article.

Abbreviations which are essential to include in your abstract should be defined at first mention in your abstract, as well as in a footnote on the first page of your article.

Before submission we recommend that you review your use of abbreviations throughout your article to ensure that it is consistent.

Appendices

We ask you to use the following format for appendices:

- Identify individual appendices within your article using the format: A, B, etc.
- Give separate numbering to formulae and equations within appendices using formats such as Eq. (A.1), Eq. (A.2), etc. and in subsequent appendices, Eq. (B.1), Eq. (B. 2) etc. In a similar way, give separate numbering to tables and figures using formats such as Table A.1; Fig. A.1, etc.

Acknowledgements

Include any individuals who provided you with help during your research, such as help with language, writing or proof reading, in the acknowledgements section. Include acknowledgements **only** in the **title page** since this journal follows a double anonymized peer review process. Do not add it as a footnote to your title.

Author contributions: CRediT

Corresponding authors are required to acknowledge co-author contributions using CRediT (Contributor Roles Taxonomy) roles:

- Conceptualization
- Data curation
- Formal analysis
- Funding acquisition
- Investigation
- Methodology
- Project administration
- Resources
- Software
- Supervision
- Validation
- Visualization
- Writing – original draft
- Writing – review and editing

Not all CRediT roles will apply to every manuscript and some authors may contribute through multiple roles.

We advise you to read more about CRediT and view an example of a CRediT author statement.

Funding sources

Authors must disclose any funding sources who provided financial support for the conduct of the research and/or preparation of the article. The role of sponsors, if any, should be declared in relation to the study design, collection, analysis and interpretation

of data, writing of the report and decision to submit the article for publication. If funding sources had no such involvement this should be stated in your submission.

List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants, scholarships and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, it is recommended to include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

References within text

Any references cited within your article should also be present in your reference list and vice versa. Some guidelines:

- References cited in your abstract must be given in full.
- We recommend that you do not include unpublished results and personal communications in your reference list, though you may mention them in the text of your article.
- Any unpublished results and personal communications included in your reference list must follow the standard reference style of the journal. In substitution of the publication date add "unpublished results" or "personal communication."
- References cited as "in press" imply that the item has been accepted for publication.

Linking to cited sources will increase the discoverability of your research.

Before submission, check that all data provided in your reference list are correct, including any references which have been copied. Providing correct reference data allows us to link to abstracting and indexing services such as Scopus, Crossref and PubMed. Any incorrect surnames, journal or book titles, publication years or pagination within your references may prevent link creation.

We encourage the use of Digital Object Identifiers (DOIs) as reference links as they provide a permanent link to the electronic article referenced. See the example below, though be aware that the format of such citations should be adapted to follow the style of other references in your paper.

DOI link example (for an article not yet in an issue): VanDecar J.C., Russo R.M., James D.E., Ambeh W.B., Franke M. (2003). Aseismic continuation of the Lesser Antilles slab beneath northeastern Venezuela. Journal of Geophysical Research, https://doi.org/10.1029/2001JB000884.

Reference style

Indicate references by adding a number within square brackets in the text. You can refer to author names within your text, but you must always give the reference number, e.g., "as demonstrated [3,6]. Barnaby and Jones [8] obtained a different result ....".

Number references in the order they appear in your article.

Examples:

Reference to a journal publication:

[1] J. van der Geer, T. Handgraaf, R.A. Lupton, The art of writing a scientific article, J. Sci. Commun. 163 (2020) 51 – 59. https://doi.org/10.1016/j.sc.2020.00372.

Reference to a journal publication with an article number:

[2] J. van der Geer, T. Handgraaf, R.A. Lupton, 2022. The art of writing a scientific article. Heliyon. 19, e00205. https://doi.org/10.1016/j.heliyon.2022.e00205.

Reference to a book:

[3] W. Strunk Jr., E.B. White, The Elements of Style, fourth ed., Longman, New York, 2000.

Reference to a chapter in a book:

[4] G.R. Mettam, L.B. Adams, How to prepare an electronic version of your article, in: B.S. Jones, R.Z. Smith (Eds.), Introduction to the Electronic Age, E-Publishing Inc., New York, 2020, pp. 281 - 304.

Reference to a website:

[5] Cancer Research UK, Cancer statistics reports for the UK. http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/, 2023 (accessed 13 March 2023).

Reference to a dataset:

[6] M. Oguro, S. Imahiro, S. Saito, T. Nakashizuka, Mortality data for Japanese oak wilt disease and surrounding forest compositions [dataset], Mendeley Data, v1, 2015. https://doi.org/10.1234/abc12nb39r.1.

Reference to software:

[7] E. Coon, M. Berndt, A. Jan, D. Svyatsky, A. Atchley, E. Kikinzon, D. Harp, G. Manzini, E. Shelef, K. Lipnikov, R. Garimella, C. Xu, D. Moulton, S. Karra, S. Painter, E. Jafarov, S. Molins, Advanced Terrestrial Simulator (ATS) v0.88 [software], Zenodo, March 25, 2020. https://doi.org/10.1234/zenodo.3727209.

Journal abbreviations

We ask you to abbreviate journal names according to the List of Title Word Abbreviations (LTWA).

Web references

When listing web references, as a minimum you should provide the full URL and the date when the reference was last accessed. Additional information (e.g. DOI, author names, dates or reference to a source publication) should also be provided, if known.

You can list web references separately under a new heading directly after your reference list or include them in your reference list.

Data references

We encourage you to cite underlying or relevant datasets within article text and to list data references in the reference list.

When citing data references, you should include:

- author name(s)
- dataset title
- data repository
- version (where available)
- year
- global persistent identifier

Add [dataset] immediately before your reference. This will help us to properly identify the dataset. The [dataset] identifier will not appear in your published article.

Preprint references

We ask you to mark preprints clearly. You should include the word "preprint" or the name of the preprint server as part of your reference and provide the preprint DOI.

Where a preprint has subsequently become available as a peer-reviewed publication, use the formal publication as your reference.

If there are preprints that are central to your work or that cover crucial developments in the topic, but they are not yet formally published, you may reference the preprint.

Reference management software

Most Elsevier journals have their reference template available in popular reference management software products. These include products that support Citation Style Language (CSL) such as Mendeley Reference Manager.

If you use a citation plug-in from these products, select the relevant journal template and all your citations and bibliographies will automatically be formatted in the journal style. We advise you to remove all field codes before submitting your manuscript to any reference management software product.

If a template is not available for this journal, follow the format given in examples in the reference style section of this Guide for Authors.