

Bilateral Common Carotid Intima-Media Thickness and Plaque Topography Across Ischemic Infarction, Transient Ischemic Attack, and Intracerebral Hemorrhage: A Multivariable Carotid Phenotyping Study

Ashis Kumar Saha¹, Prasun Chatterjee², Moyukh Mukherjee³

¹Professor & Head, Department of Medicine,
Jagannath Gupta Institute of Medical Sciences, Budge Budge, Kolkata

²Assistant Professor, Department of Medicine,
Jagannath Gupta Institute of Medical Sciences, Budge Budge, Kolkata

³Post Graduate trainee, Department of Medicine,
Jagannath Gupta Institute of Medical Sciences, Budge Budge, Kolkata

Corresponding author: Ashis Kumar Saha

DOI: <https://doi.org/10.52403/ijhsr.20261012>

Received: 04/06/2026; Revised: 02/09/2026; Accepted: 24/10/2026

ABSTRACT

Introduction: Carotid intima-media thickness (cIMT) and focal plaque represent related but distinct markers of vascular injury. Their distribution across ischemic infarction (INF), transient ischemic attack (TIA), and intracerebral hemorrhage (ICH) may clarify differences in cerebrovascular phenotypes. Because conventional risk factors overlap substantially, integrated carotid phenotyping may provide useful mechanistic information beyond isolated vascular measurements.

Aims and objectives: To compare bilateral common carotid artery cIMT, inter-side asymmetry, plaque prevalence, laterality and topography across INF, TIA and ICH, and assess their independent association with clinical presentation.

Materials and methods: This hospital-based study included 443 patients with cerebrovascular presentations: 238 INF, 113 TIA and 92 ICH. All underwent neuroimaging, laboratory evaluation and carotid Doppler ultrasonography. Right, left, mean and maximum CCA-IMT, asymmetry and plaque characteristics were analyzed. Kruskal-Wallis and chi-square tests, multinomial logistic regression, restricted cubic splines, sensitivity analyses and AUROC assessment with 10-fold cross-validation were performed.

Results: Mean bilateral cIMT was similar in INF, TIA and ICH (1.10 ± 0.23 , 1.09 ± 0.25 and 1.09 ± 0.26 mm; $P=0.751$), with no significant difference in other cIMT measures. Among 374 patients with interpretable plaque coding, plaque prevalence was 60.6%, 42.6% and 57.1%, respectively ($P=0.014$), driven by INF versus TIA (Holm-adjusted $P=0.011$). Mean cIMT was not independently associated with INF or TIA versus ICH, but was associated with plaque presence (aOR 1.60 per SD, 95% CI 1.24-2.07; $P<0.001$). Cross-validated macro-AUROC was 0.485.

Conclusion: Diffuse carotid wall thickening did not discriminate cerebrovascular presentation, whereas focal plaque prevalence differed, particularly between infarction and TIA. cIMT remains a marker of underlying carotid atherosclerotic burden rather than a stand-alone classifier of presentation subtype.

Keywords: Bilateral Common Carotid Intima-medial thickness, Ischemic infarction, Transient ischemic attack, Intracerebral hemorrhage, carotid phenotyping study.

INTRODUCTION

Stroke remains one of the leading causes of death and long-term disability worldwide, with a disproportionate burden in low- and middle-income countries. [1] Contemporary Global Burden of Disease analyses emphasize that ischemic stroke and intracerebral hemorrhage (ICH) are biologically distinct cerebrovascular entities that share several vascular risk factors but differ in pathogenesis, recurrence profile, preventive strategy, and clinical outcome. [1-3] Transient ischemic attack (TIA), although defined by transient neurological dysfunction without established infarction, occupies an important position in the same vascular continuum because it frequently reflects unstable atherosclerotic, thromboembolic, or small-vessel disease and identifies patients at heightened risk of cerebral infarction. [2] Accurate phenotyping of systemic and cervico-cerebral vascular disease across these presentations may therefore improve mechanistic understanding and refine risk stratification beyond conventional clinical factors.

Carotid ultrasonography offers a non-invasive, reproducible, widely available method of evaluating subclinical and established atherosclerosis. Common carotid artery intima-media thickness (CCA-IMT) is a composite measure of the intimal and medial layers and reflects the cumulative influence of ageing, blood pressure, metabolic factors, smoking, and atherosclerotic remodeling. [4-6] Standardized measurement protocols and consensus definitions have established CCA-IMT and focal carotid plaque as related but non-identical vascular phenotypes. [4,5] Population-based studies have consistently

demonstrated associations between greater carotid IMT and subsequent cardiovascular and cerebrovascular events, although the incremental predictive value of IMT beyond conventional risk models varies across populations. [7-9] Importantly, plaque burden and plaque characteristics often provide complementary or stronger information than IMT alone, suggesting that structural carotid assessment should not be restricted to a single wall-thickness measurement. [10]

Evidence also indicates that the relationship between carotid atherosclerosis and cerebrovascular disease is not uniform across stroke subtypes. In the ARIC cohort, greater carotid wall thickness was associated with incident ischemic and hemorrhagic stroke, but the strength of association differed among lacunar, non-lacunar, cardioembolic, and hemorrhagic events. [11] Similar observations from the Tromsø and Rotterdam studies showed that carotid plaque burden and plaque distribution predicted ischemic stroke, with plaque measures in some analyses outperforming IMT. [10,12] Studies directly comparing cerebral infarction with ICH have reported higher CCA-IMT in ischemic phenotypes, particularly large-vessel or lacunar infarction, than in hemorrhagic stroke, [13,14] while other cohort data suggest that increased IMT may also be associated with ICH as a marker of long-standing hypertensive and systemic vascular injury. [15] A systematic review consequently found that increased CCA-IMT is more strongly associated with ischemic stroke than ICH and may also differentiate large-vessel from small-vessel ischemic disease. [16]

The distinction between TIA and completed ischemic infarction is equally relevant.

Ultrasonographic studies have demonstrated that carotid atherosclerotic burden and plaque morphology are associated with symptomatic cerebrovascular disease, [17] while vessel-wall imaging has shown that plaque size, wall thickness, intraplaque hemorrhage, and other vulnerability features can differ between TIA and ischemic stroke. [18] Carotid plaque location may also carry biological significance. Plaque at the bifurcation or internal carotid artery reflects focal atherosclerotic susceptibility at sites of disturbed flow, whereas bilateral or multisegment plaque may indicate more extensive systemic atherosclerosis. [12,17] Accordingly, assessment of plaque topography together with bilateral CCA-IMT could provide a more comprehensive carotid phenotype than either variable considered alone. [19,20]

Despite this evidence, relatively few studies have evaluated bilateral CCA-IMT, inter-side asymmetry, and plaque topography simultaneously across ischemic infarction, TIA, and spontaneous ICH within a single multivariable framework. Many previous studies have focused on case-control comparisons with healthy controls, examined only ischemic stroke subtypes, or used isolated IMT or plaque measurements without integrating vascular risk factors, glycemic status, lipid variables, renal function, and blood pressure. [13,14,19,21] This limitation is important because IMT and plaque are strongly influenced by age, hypertension, diabetes, smoking, dyslipidemia, and renal dysfunction, making multivariable adjustment essential when attributing differences to cerebrovascular phenotype itself. [22,23]

The present study therefore aims to characterize and compare bilateral common carotid IMT and plaque topography among patients presenting with ischemic infarction, TIA, and intracerebral hemorrhage. By integrating right and left CCA-IMT, mean and maximum IMT, inter-side asymmetry, plaque presence and distribution, and major vascular risk factors in a multivariable

model, the study seeks to determine whether distinct carotid phenotypes are associated with different cerebrovascular presentations. Such a phenotype-based approach may clarify the relative contributions of systemic atherosclerosis and hypertensive vascular injury across ischemic and hemorrhagic cerebrovascular disease and provide a practical framework for future risk-stratification studies using routinely available carotid Doppler ultrasonography. [16,20]

Aim of the Study

To characterize and compare carotid atherosclerotic phenotypes among patients presenting with ischemic infarction (INF), transient ischemic attack (TIA), and intracerebral hemorrhage (ICH), using bilateral common carotid artery intima-media thickness (CCA-IMT) and carotid plaque presence, laterality, and anatomical distribution, and to determine whether these carotid structural markers are independently associated with the type of cerebrovascular presentation after adjustment for major vascular risk factors.

Primary Objective

To determine whether bilateral CCA-IMT and carotid plaque phenotype differ significantly among patients with ischemic infarction, TIA, and ICH, and whether these carotid parameters remain independently associated with cerebrovascular presentation in multivariable analysis.

Secondary Objectives

- To compare right CCA-IMT and left CCA-IMT among INF, TIA, and ICH groups.
- To compare derived bilateral IMT measures, including mean CCA-IMT, maximum CCA-IMT, and absolute right-left IMT asymmetry, across the three clinical groups.
- To determine and compare the prevalence of carotid plaque in INF, TIA, and ICH.

- To compare plaque laterality (right-sided, left-sided, unilateral, or bilateral) and plaque topography, including CCA, carotid bifurcation, and ICA involvement, across the three presentations.
- To evaluate the association of conventional vascular risk factors—age, sex, hypertension, diabetes mellitus, smoking, systolic and diastolic blood pressure, and glycemic status—with carotid IMT and plaque phenotype.
- To assess the relationship of lipid-profile parameters, including total cholesterol, LDL-C, HDL-C, triglycerides, TC/HDL ratio and, where appropriate, derived non-HDL-C or TG/HDL ratio, with carotid IMT and plaque burden.
- To assess the relationship of renal-function parameters, particularly serum creatinine and estimated glomerular filtration rate when calculated, with carotid structural abnormalities.
- To determine whether carotid IMT and plaque variables can distinguish ischemic presentations (INF and TIA) from hemorrhagic presentation (ICH).
- To compare carotid structural phenotype between completed ischemic infarction and TIA to explore whether greater carotid atherosclerotic burden is associated with established cerebral infarction.
- To construct an adjusted multivariable model identifying carotid and clinical factors independently associated with INF, TIA, and ICH presentation.

MATERIALS AND METHODS

A hospital-based observational, cross-sectional analysis was conducted at Jagannath Gupta Institute of Medical Sciences and Hospital, Budge Budge, West Bengal, India, as this is a retrospective study, it didn't require any ethical approval from the local Ethical committee.

Patients who presented to the hospital with clinical features suggestive of an acute cerebrovascular event and who underwent

diagnostic neuroimaging and carotid Doppler assessment formed the study population. Hospital clinical records, neuroimaging findings, laboratory reports, and carotid ultrasonography records were reviewed and linked for the analysis. The final analytical cohort comprised 443 patients: 238 with ischemic infarction (INF), 113 with transient ischemic attack (TIA), and 92 with intracerebral hemorrhage (ICH). The source manuscript did not record whether recruitment was consecutive, convenience-based, or retrospective; accordingly, no unverified sampling strategy was asserted.

Eligibility criteria - inclusion

Patients were included in the analyzed cohort when (1) they had presented with symptoms or signs suggestive of a cerebrovascular event; (2) their clinical assessment and brain imaging had supported assignment to one of the three study categories—INF, TIA, or ICH; and (3) a carotid Doppler assessment had been recorded. The diagnostic categories were mutually exclusive for analysis. These criteria reflected the records included in the reported final dataset rather than a separately documented prospective screening protocol.

Eligibility criteria - exclusion

Patients without an assignable INF, TIA, or ICH diagnosis were not included in the final cohort; no neurologically normal/non-CVA comparison group was analyzed. Records from other cerebrovascular categories or with insufficient information to establish one of these three diagnostic groups were not represented in the reported analysis. Importantly, missing individual laboratory values, a missing right-sided cIMT value, or uninterpretable plaque coding did not automatically exclude a patient from the 443-person cohort: such records were omitted only from analyses that required the unavailable variable. No additional clinical exclusion criteria, including age cutoffs, prior stroke, carotid intervention, trauma, or coexisting illnesses, were specified in the

source records and therefore could not be verified.

Clinical classification and neuroimaging

Patients underwent clinical neurological evaluation and brain magnetic resonance imaging, as described in the original report. Patients with imaging-supported cerebral infarction were classified as INF, whereas those with intracerebral bleeding were classified as ICH. Patients whose neurological deficits resolved and whose imaging did not demonstrate an established infarct were recorded as TIA. The source used a 24–48-hour symptom-resolution description for TIA; because that description did not establish a uniform contemporary tissue-based TIA definition, the final categorization was treated as the original study classification. The exact imaging sequences, timing from symptom onset, and adjudication procedure were not available for independent confirmation.

Sample collection and laboratory evaluation:

During the hospital evaluation, blood specimens were obtained for routine investigations documented in the study records, including complete blood count, lipid profile, liver-function tests, urea, serum creatinine, and electrolytes. The regression dataset additionally contained glycemic variables, including HbA1c, and lipid-derived measures. Demographic characteristics, vascular risk-factor history, smoking status, blood pressure, and available laboratory measurements were abstracted from the clinical dataset. The source manuscript did not state venipuncture timing, fasting duration, tube type, collection volume, processing interval, laboratory analyzer, assay methods, or whether sampling preceded treatment. Those procedural details were not retrospectively invented and should be inserted from laboratory SOPs and source documents if available.

Carotid Doppler ultrasonography and variable derivation:

Carotid Doppler ultrasonography was performed in all 443 enrolled patients. Recorded right and left common carotid artery intima-media thickness (CCA-IMT) values were expressed in millimetres. Mean bilateral cIMT was calculated as the arithmetic mean of the right and left readings when both were available; maximum cIMT was the higher side-specific value, and cIMT asymmetry was the absolute right–left difference. Plaque presence, right/left or unilateral/bilateral involvement, and recorded anatomical location (CCA, carotid bifurcation, ICA, or other) were summarized when the source code was interpretable. Plaque entries that were blank or non-standard were treated as missing, not as plaque absent. The source did not specify scanner model, probe frequency, whether readings used far-wall measurements, cardiac gating, blinding, replicate measurements, or an interobserver agreement protocol; these technical details require confirmation rather than assumption. The study dataset contained 443 classified patients. Right CCA-IMT was unavailable for one participant; LDL-C was unavailable for 36 participants. The primary covariate-adjusted complete-case model therefore included 404 participants (218 INF, 103 TIA, and 83 ICH). Plaque status was interpretable for 374 participants, with 69 blank or non-standard plaque-site entries excluded from plaque-specific analyses. The joint plaque-valid complete-case sensitivity models used 335 participants. Seven records had at least one CCA-IMT value below 0.30 mm and were investigated in a dedicated sensitivity analysis without silently altering their original values. All reported denominators were matched to the relevant analysis, and missing data were not imputed.

Statistical Analysis

1. Group-wise Comparison of Carotid IMT

Right CCA-IMT, left CCA-IMT, mean bilateral cIMT, maximum cIMT, and cIMT asymmetry were compared among the INF, TIA, and ICH groups. For the normally distributed variables, one-way analysis of variance (ANOVA) was used. When the overall ANOVA is statistically significant, appropriate post-hoc pairwise comparisons were performed with correction for multiple testing. For non-normally distributed variables, the Kruskal-Wallis test was used, followed by adjusted pairwise comparisons where appropriate.

2. Comparison of Carotid Plaque Patterns

The prevalence and distribution of carotid plaque were compared among the three clinical groups using the chi-square test. When expected cell frequencies are small, Fisher's exact test or an appropriate exact/Monte Carlo test was used instead of the conventional chi-square test.

- Presence versus absence of carotid plaque
- Unilateral versus bilateral plaque
- Right-sided versus left-sided plaque
- CCA plaque
- Carotid bifurcation plaque
- ICA plaque
- Multisite plaque involvement

3. Multinomial Logistic Regression

A multinomial logistic regression model was constructed with cerebrovascular presentation (INF, TIA, or ICH) as the dependent variable. One clinical group, preferably ICH, was specified as the reference category so that adjusted associations of carotid structural characteristics with INF and TIA relative to ICH can be quantified. Potential adjustment variables included age, sex, hypertension, diabetes mellitus, smoking, systolic blood pressure, HbA1c, LDL-C or non-HDL-C, triglyceride/HDL-C ratio, and serum creatinine/eGFR, subject to data completeness and assessment of multicollinearity. Results were expressed as adjusted odds ratios (aORs) with 95% confidence intervals and P values.

4. Standardized cIMT Effect Analysis

To permit clinically meaningful comparison of effect sizes, cIMT was additionally standardized. Adjusted odds ratios were therefore reported per 1-SD increase in cIMT rather than solely per 1-mm increase. This approach allows the magnitude of association between carotid wall thickness and cerebrovascular presentation to be compared across models and cIMT measurements.

- Right CCA-IMT
- Left CCA-IMT
- Mean bilateral cIMT
- Maximum bilateral cIMT

5. Assessment of Nonlinear Association

The possibility of a nonlinear relationship between cIMT and cerebrovascular presentation was investigated using restricted cubic spline (RCS) modeling. Mean or maximum cIMT was entered into the regression model using restricted cubic splines, with knots placed at conventional quantiles of the cIMT distribution. Both the overall association and evidence for nonlinearity were evaluated. Spline curves displayed adjusted odds ratios with 95% confidence intervals across the observed range of cIMT and were examined for thresholds or nonlinear increases in the association with ischemic presentations.

6. Sensitivity Analyses for cIMT and Plaque

Because increased cIMT and carotid plaque represent related manifestations of carotid vascular disease and could demonstrate collinearity, sensitivity analyses were performed using separate multivariable models. Consistency of effect estimates across these models were examined to determine whether cIMT and plaque provide independent information regarding cerebrovascular presentation.

- Model A: cIMT variables without carotid plaque variables.
- Model B: carotid plaque presence/topography without cIMT.
- Model C: both cIMT and plaque variables, provided variance inflation

factors and other collinearity diagnostics remain acceptable.

7. Secondary Pairwise Analyses

Secondary regression analyses included the following clinically relevant comparisons:

- INF versus TIA, assessing whether carotid structural burden differentiates completed cerebral infarction from transient ischemia.
- INF + TIA versus ICH, representing ischemic versus hemorrhagic cerebrovascular presentation.
- Plaque-positive versus plaque-negative patients, evaluating determinants of carotid atherosclerotic disease.

Binary logistic regression was used for these secondary dichotomous outcomes.

8. Model Diagnostics and Statistical Significance

Multi-collinearity was evaluated using correlation matrices and the variance inflation factor (VIF). Model calibration, goodness-of-fit, influential observations, and residual diagnostics were assessed where appropriate. Adjusted odds ratios were presented with 95% confidence intervals. All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. Where multiple pairwise comparisons are undertaken, an appropriate multiplicity correction was applied.

RESULTS

1. Dataset, coding, and analysis populations

Purpose. To define exactly which observations contributed to each analysis and to avoid silently imputing missing or non-standard values.

Data used. The final workbook contained 443 patients: ischemic infarction (INF) $n=238$, transient ischemic attack (TIA) $n=113$, and intracerebral hemorrhage (ICH) $n=92$. No normal/non-CVA patient was included.

- Right CCA-IMT was missing in 1 patient; left CCA-IMT was otherwise available.
- LDL-C was missing in 36 patients; therefore the primary adjusted model used complete-case analysis and contained $N=404$ patients (218 INF, 103 TIA, 83 ICH).
- Plaque status was explicitly interpretable in 374 patients. 69 plaque-site entries were blank or non-standard and were excluded only from analyses requiring plaque status/topography; they were not guessed.
- Seven patients had at least one recorded CCA-IMT <0.30 mm; a dedicated data-quality sensitivity analysis was performed after excluding these records.

Derived variables. Mean bilateral cIMT was the average of right and left CCA-IMT; maximum cIMT was the larger of the two measurements; asymmetry was the absolute right-left difference. TG/HDL ratio was calculated from the recorded triglyceride and HDL-C values. For regression, age, SBP and LDL-C were scaled to clinically interpretable units, and mean cIMT was standardized to one sample SD.

2. Groupwise comparison of carotid intima-media thickness

Research question. Do right, left, mean, maximum, or asymmetric CCA-IMT values differ among INF, TIA, and ICH?

Choice of test. The prespecified plan allowed one-way ANOVA for approximately normal data and Kruskal-Wallis testing for non-normal data. Shapiro-Wilk testing showed significant non-normality for all cIMT measures within the clinical groups; therefore Kruskal-Wallis tests were used. Levene tests did not suggest important variance heterogeneity, but the non-normality criterion determined the final test choice. The complete groupwise cIMT comparison is presented in Table 1.

Table 1. Groupwise comparison of carotid intima-media thickness among ischemic infarction, transient ischemic attack, and intracerebral hemorrhage.

cIMT variable	INF	TIA	ICH	H statistic	P value
Right CCA-IMT (mm)	Mean 1.09±0.28 Median 1.10 [1.00-1.20] n=238	Mean 1.08±0.26 Median 1.10 [1.00-1.20] n=113	Mean 1.09±0.30 Median 1.10 [1.00-1.20] n=91	0.543	0.762
Left CCA-IMT (mm)	Mean 1.12±0.24 Median 1.10 [1.00-1.20] n=238	Mean 1.11±0.29 Median 1.10 [1.00-1.20] n=113	Mean 1.10±0.26 Median 1.10 [1.00-1.30] n=92	1.335	0.513
Mean bilateral CCA-IMT (mm)	Mean 1.10±0.23 Median 1.10 [1.00-1.25] n=238	Mean 1.09±0.25 Median 1.10 [1.00-1.25] n=113	Mean 1.09±0.26 Median 1.10 [1.00-1.25] n=91	0.574	0.751
Maximum bilateral CCA-IMT (mm)	Mean 1.18±0.27 Median 1.10 [1.00-1.30] n=238	Mean 1.18±0.29 Median 1.10 [1.00-1.30] n=113	Mean 1.16±0.28 Median 1.15 [1.00-1.30] n=92	0.274	0.872
Absolute right-left IMT asymmetry (mm)	Mean 0.15±0.19 Median 0.10 [0.00-0.20] n=238	Mean 0.17±0.20 Median 0.10 [0.00-0.20] n=113	Mean 0.14±0.16 Median 0.10 [0.00-0.20] n=91	1.141	0.565

Result. No cIMT measure differed significantly across the three presentations. For the primary structural measure, mean bilateral CCA-IMT, the median was 1.10 mm in all three groups and the overall Kruskal-Wallis statistic was $H=0.574$ ($P=0.751$). Right CCA-IMT, left CCA-IMT, maximum cIMT and absolute asymmetry were also non-significant (all $P>0.50$). Because no overall cIMT test was significant, post-hoc

pairwise cIMT testing was not required. These findings are consistent across all five cIMT metrics shown in Table 1.

Interpretation. At the unadjusted level, bilateral carotid wall thickness is highly overlapping in INF, TIA, and ICH. The similarity is not confined to the mean value: maximum wall thickness and right-left asymmetry also fail to separate the groups.

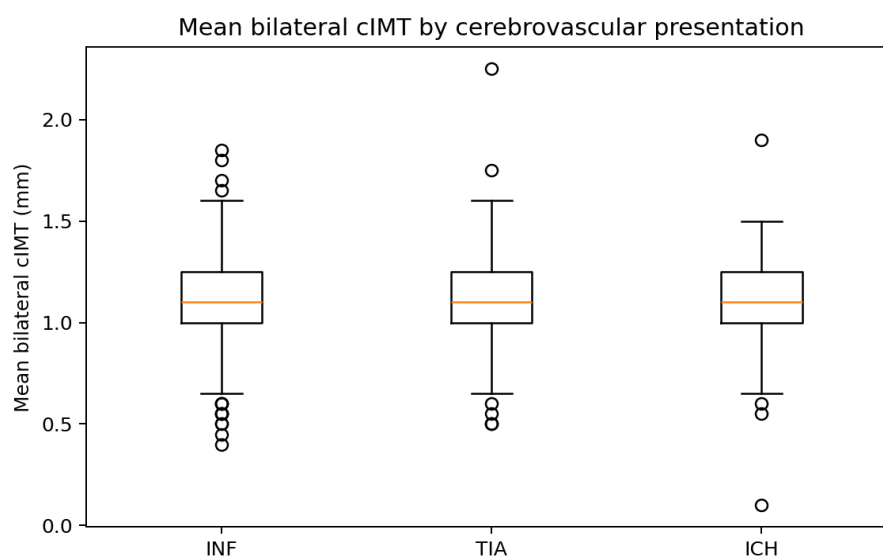


Figure 1. Distribution of mean bilateral CCA-IMT across INF, TIA, and ICH. The extensive overlap is consistent with the non-significant Kruskal-Wallis test.

3. Carotid plaque presence, laterality, and topography

Research question. Does focal carotid atherosclerotic plaque show a different prevalence or anatomical pattern across the three cerebrovascular presentations?

Statistical method. Only patients with an explicit interpretable plaque code were analyzed. Plaque absent versus present was

compared using Pearson chi-square. Plaque laterality (none/unilateral/bilateral) and simplified topography (no plaque/ICA/CCA-or-other) were also compared using chi-square. Pairwise plaque-presence comparisons were Holm-adjusted for multiplicity. Group-specific plaque counts and prevalence are summarized in Table 2.

Table 2. Carotid plaque prevalence among patients with interpretable plaque coding, stratified by cerebrovascular presentation.

Group	Plaque present	Plaque absent	Valid n	Prevalence
INF	123	80	203	60.6%
TIA	40	54	94	42.6%
ICH	44	33	77	57.1%

Overall plaque-presence result. Plaque prevalence differed across groups: $\chi^2=8.585$, $df=2$, $P=0.014$. Prevalence among valid plaque-coded patients was 60.6% in INF, 42.6% in TIA, and 57.1% in ICH. The underlying counts and valid denominators are shown in Table 2.

- INF vs TIA: $\chi^2=8.442$; raw $P=0.004$; Holm-adjusted $P=0.011$.
- INF vs ICH: $\chi^2=0.276$; raw $P=0.599$; Holm-adjusted $P=0.599$.
- TIA vs ICH: $\chi^2=3.605$; raw $P=0.058$; Holm-adjusted $P=0.115$.

Laterality. The distribution of no plaque, unilateral plaque and bilateral plaque

approached but did not reach conventional statistical significance ($\chi^2=9.244$, $df=4$, $P=0.055$).

Topography. The simplified anatomical distribution of no plaque, ICA plaque and CCA/other plaque was also not statistically different ($\chi^2=8.821$, $df=4$, $P=0.066$).

Interpretation. The main plaque signal is a difference in whether plaque is present at all, driven primarily by the higher plaque prevalence in INF compared with TIA. The present dataset does not provide sufficiently strong evidence that laterality or anatomic topography itself differs among the three presentation groups.

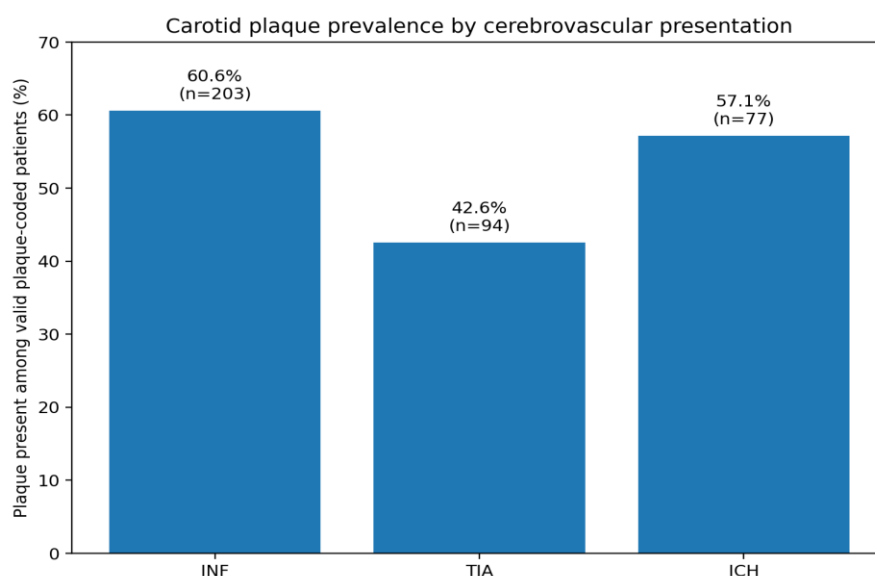


Figure 2. Carotid plaque prevalence among patients with explicit interpretable plaque coding. Percentages use the valid plaque-coded denominator within each presentation group.

4. Primary multinomial logistic regression

Research question. After accounting for conventional vascular risk factors, is mean bilateral cIMT independently associated with whether a patient presents with INF, TIA, or ICH?

Model specification. Cerebrovascular presentation was the three-level dependent variable. ICH was the reference outcome. The model included age, sex, hypertension, diabetes, smoking, systolic blood pressure, HbA1c, LDL-C, TG/HDL ratio, creatinine, and mean bilateral cIMT. The cIMT effect was expressed per one-standard-deviation

increase. Complete-case N was 404. Odds ratios therefore compare INF with ICH and TIA with ICH at the same values of the other covariates. The adjusted INF-versus-ICH and TIA-versus-ICH estimates are presented in Tables 3 and 4, respectively.

Overall model. The overall likelihood-ratio test was not significant ($P=0.617$); McFadden pseudo- R^2 was 0.024, AIC 841.8, and BIC 937.8. The small pseudo- R^2 and non-significant global test indicate limited separation of the three presentations by this covariate set.

INF vs ICH

Table 3. Primary adjusted multinomial logistic regression: ischemic infarction versus intracerebral hemorrhage.

Predictor	Adjusted OR	95% CI	P value
Age per 10 y	0.93	0.76-1.15	0.518
Male sex	1.36	0.75-2.47	0.313
Hypertension	0.90	0.46-1.78	0.771
Diabetes	0.90	0.42-1.92	0.784
Smoking	1.20	0.55-2.60	0.649
SBP per 10 mmHg	0.97	0.87-1.09	0.643
HbA1c per 1%	1.19	0.77-1.85	0.428
LDL-C per 10 mg/dL	0.96	0.90-1.02	0.163
TG/HDL ratio per 1	1.04	0.89-1.22	0.596
Creatinine per 1 mg/dL	0.45	0.22-0.93	0.032
cIMT per 1 SD	1.07	0.82-1.41	0.607

TIA vs ICH

Table 4. Primary adjusted multinomial logistic regression: transient ischemic attack versus intracerebral hemorrhage.

Predictor	Adjusted OR	95% CI	P value
Age per 10 y	0.97	0.76-1.24	0.830
Male sex	1.18	0.60-2.35	0.631
Hypertension	1.04	0.49-2.21	0.921
Diabetes	0.77	0.32-1.82	0.547
Smoking	1.38	0.58-3.31	0.468
SBP per 10 mmHg	0.90	0.79-1.03	0.117
HbA1c per 1%	1.17	0.71-1.93	0.544
LDL-C per 10 mg/dL	0.91	0.85-0.98	0.015
TG/HDL ratio per 1	1.04	0.87-1.24	0.652
Creatinine per 1 mg/dL	0.67	0.31-1.45	0.311
cIMT per 1 SD	1.06	0.78-1.45	0.705

Primary cIMT result. A one-SD increase in mean bilateral cIMT was not associated with INF versus ICH (aOR 1.07, 95% CI 0.82-1.41; $P=0.607$) or TIA versus ICH (aOR 1.06, 95% CI 0.78-1.45; $P=0.705$). Full

adjusted estimates are provided in Tables 3 and 4.

Other covariates. Creatinine was inversely associated with INF versus ICH and LDL-C was inversely associated with TIA versus

ICH in this fitted model. Because the global multinomial model was not statistically significant and multiple covariates were examined, these isolated associations should be treated as exploratory rather than as definitive independent findings.

Interpretation. Adjustment for demographic, hemodynamic, glycemic, lipid, smoking and renal variables does not reveal a hidden association between mean cIMT and the clinical presentation category.

This agrees with the unadjusted groupwise cIMT analysis.

5. Adjusted odds ratios per 1-SD increase in each cIMT measure

Purpose. To determine whether the negative result depends on which bilateral cIMT summary is chosen, right, left, mean and maximum cIMT were each standardized and entered separately into otherwise comparable multinomial models. The standardized cIMT effects are summarized in Table 5.

Table 5. Adjusted odds ratios for cerebrovascular presentation per 1-SD increase in alternative carotid intima-media thickness measures.

cIMT measure	N	1 SD (mm)	INF vs ICH aOR (95% CI)	P	TIA vs ICH aOR (95% CI)	P
Right CCA-IMT	404	0.270	1.01 (0.78-1.32)	0.932	1.04 (0.77-1.41)	0.801
Left CCA-IMT	405	0.264	1.13 (0.85-1.49)	0.395	1.07 (0.78-1.47)	0.663
Mean bilateral CCA-IMT	404	0.238	1.07 (0.82-1.41)	0.607	1.06 (0.78-1.45)	0.705
Maximum bilateral CCA-IMT	405	0.277	1.06 (0.80-1.39)	0.687	1.09 (0.80-1.50)	0.574

Interpretation. None of the standardized right, left, mean, or maximum cIMT effects reached statistical significance for either contrast. The consistency across alternative cIMT summaries argues against the possibility that the null result is simply caused by an unfavorable choice of cIMT metric.

6. Restricted cubic spline analysis of mean bilateral cIMT

Research question. Could cIMT have a nonlinear association with presentation that is missed by a single linear odds ratio?

Method. Mean bilateral cIMT was modeled using restricted cubic spline terms in the same adjusted multinomial framework

(N=404). The reference was the median cIMT of 1.10 mm, where the relative odds ratio is defined as 1.00. The analysis tested both the overall contribution of the spline and the additional nonlinear contribution beyond a simple linear cIMT term.

Overall result. Adding the spline terms was not significant (likelihood-ratio $P=0.748$), and the specific test for nonlinearity was also non-significant ($LR=4.819$, $df=6$, $P=0.567$). Thus there is no statistical evidence of a threshold, U-shaped relation, or other nonlinear dose-response pattern. Representative spline-derived odds ratios across the observed cIMT range are shown in Table 6.

Table 6. Restricted cubic spline estimates for mean bilateral carotid intima-media thickness relative to the median reference value.

Mean cIMT (mm)	INF vs ICH OR	95% CI	TIA vs ICH OR	95% CI
0.80	0.69	0.34-1.42	0.87	0.38-2.02
1.00	0.94	0.74-1.19	1.03	0.77-1.38
1.10	1.00	1.00-1.00	1.00	1.00-1.00
1.25	0.91	0.67-1.22	0.82	0.59-1.16
1.35	0.76	0.43-1.37	0.69	0.36-1.34

Interpretation. The fitted curves deviate modestly from 1.0 at the extremes, but the confidence intervals are wide and cross 1.0 throughout the clinically populated cIMT

range. The apparent curvature is therefore compatible with random sampling variability rather than a reproducible biologic threshold.

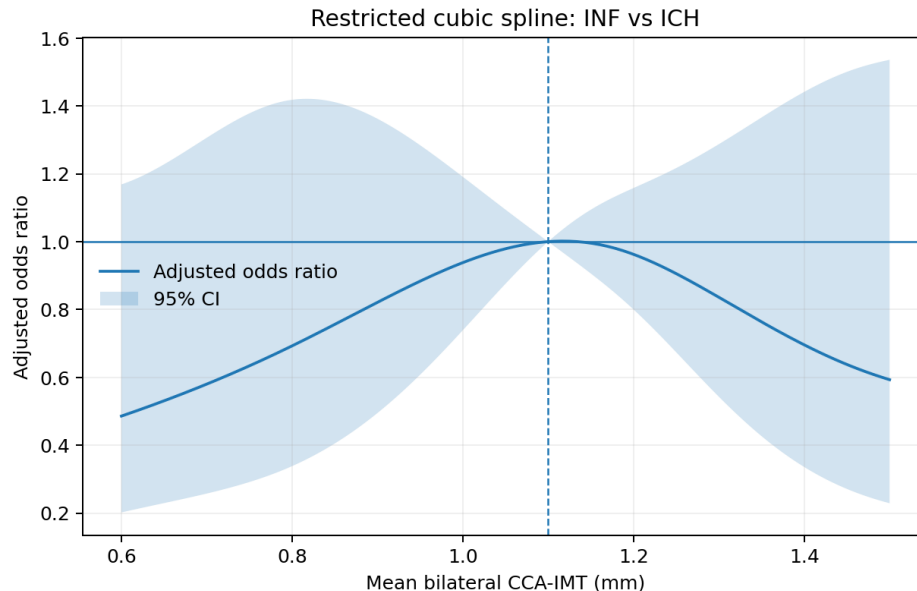


Figure 3. Adjusted restricted cubic spline for INF versus ICH. The solid line is the relative odds ratio and the shaded band is the 95% confidence interval; the vertical dashed line marks the median cIMT reference.

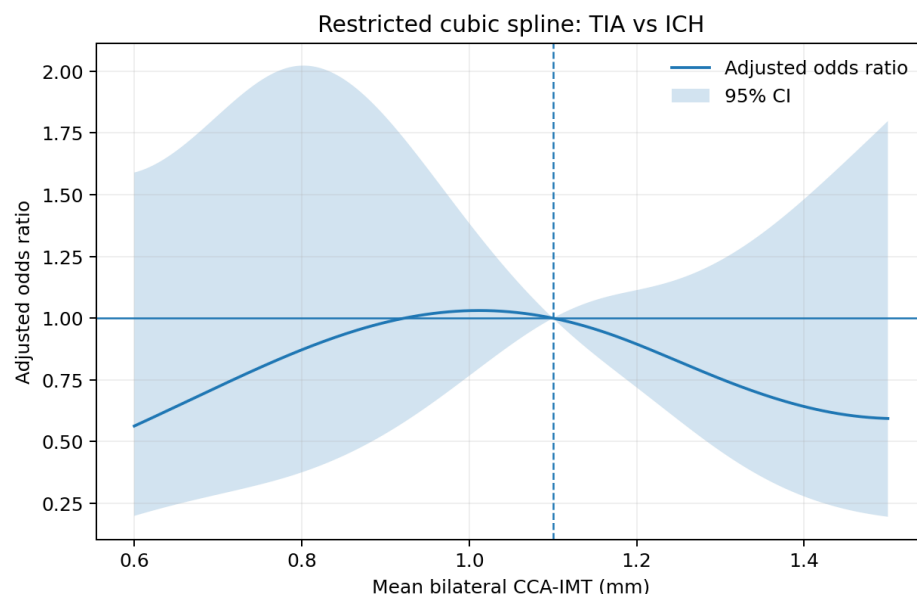


Figure 4. Adjusted restricted cubic spline for TIA versus ICH. The broad confidence bands at the distribution tails indicate limited precision at extreme cIMT values.

7. Sensitivity analysis separating plaque from cIMT

Rationale. cIMT and focal plaque are related manifestations of carotid vascular disease. Entering strongly related markers into the same model can make coefficients unstable.

Therefore, the prespecified sensitivity strategy compared a cIMT model, a plaque model, and a combined model on the same complete-case plaque-valid subset (N=335). The cIMT-only, plaque-only, and combined

sensitivity models are summarized in Table 7.

Table 7. Sensitivity models separating carotid intima-media thickness and plaque effects in the common plaque-valid complete-case subset.

Model	AIC	INF vs cIMT/plaque	ICH: P	TIA vs cIMT/plaque	ICH: P
A: cIMT only	699.9	cIMT 1.08 (0.81-1.44)	0.617	cIMT 1.15 (0.82-1.61)	0.430
B: plaque only	693.9	Plaque 1.42 (0.78-2.61)	0.252	Plaque 0.69 (0.35-1.38)	0.295
C: cIMT + plaque	696.7	cIMT 1.04; plaque 1.40	0.793; 0.291	cIMT 1.19; plaque 0.64	0.317; 0.219

Collinearity assessment. In the combined model, the VIF was only 1.14 for cIMT and 1.16 for plaque, indicating no problematic cIMT-plaque collinearity.

Interpretation. Neither cIMT nor plaque presence was independently significant in these adjusted presentation models. Although the plaque-only model had a somewhat lower AIC within the common subset, all three overall model tests were non-significant; therefore the AIC difference

should not be interpreted as proof that plaque is a clinically adequate classifier.

8. Secondary pairwise adjusted analyses

Purpose. The multinomial model asks about all three presentations simultaneously. Secondary binary models tested clinically focused contrasts: completed infarction versus TIA; all ischemic presentations versus ICH; and cIMT as a determinant of plaque presence. Results of these clinically focused secondary comparisons are shown in Table 8.

Table 8. Secondary pairwise adjusted analyses of mean bilateral carotid intima-media thickness.

Contrast/outcome	N	aOR per 1-SD mean cIMT	95% CI	P value	Overall model P
INF vs TIA (INF=1)	321	1.02	0.79-1.32	0.869	0.756
Ischemic (INF+TIA) vs ICH	404	1.07	0.83-1.39	0.613	0.358
Plaque present vs absent	335	1.60	1.24-2.07	<0.001	<0.001

Interpretation. Mean cIMT did not distinguish INF from TIA and did not distinguish the combined ischemic group from ICH. In contrast, mean cIMT was strongly associated with the presence of carotid plaque (aOR 1.60 per SD, 95% CI 1.24-2.07; P<0.001). This is an important internal-consistency finding: thicker carotid walls track focal carotid atherosclerosis even though cIMT does not discriminate the clinical presentation groups.

9. AUROC and ROC-curve analysis

Why AUROC was added. Odds ratios assess association, whereas the area under the receiver-operating-characteristic curve assesses discrimination: how well fitted probabilities rank patients with one outcome above patients without that outcome.

Because the primary model has three outcome categories, one-vs-rest ROC curves were calculated for INF, TIA and ICH. These are exploratory discrimination analyses; the primary scientific model remains an association model.

AUROC estimation. The main multinomial model used the same complete-case N=404. Apparent AUROCs were calculated from model-predicted probabilities. Ninety-five percent confidence intervals were estimated using 5,000 stratified nonparametric bootstrap resamples of the observed outcomes and fitted probabilities. Macro-average AUROC gives equal weight to the three classes; weighted-average AUROC weights classes by their observed frequency. Apparent class-specific and summary AUROCs are presented in Table 9.

Table 9. Apparent one-vs-rest AUROC performance of the adjusted multinomial model.

ROC contrast	AUROC	95% CI	Interpretation
INF vs rest	0.567	0.513-0.622	Poor discrimination
TIA vs rest	0.598	0.535-0.657	Poor discrimination
ICH vs rest	0.626	0.555-0.693	Modest discrimination
Macro-average one-vs-rest	0.597	0.553-0.641	Poor discrimination
Weighted-average one-vs-rest	0.587	0.542-0.631	Poor discrimination

Main AUROC result. The macro-average apparent AUROC was 0.597 (95% CI 0.553-0.641). ICH-versus-rest had the highest class-specific AUROC at 0.626, but this is

still only modest discrimination. INF-versus-rest was 0.567, and TIA-versus-rest was 0.598. The complete apparent AUROC profile is shown in Table 9.

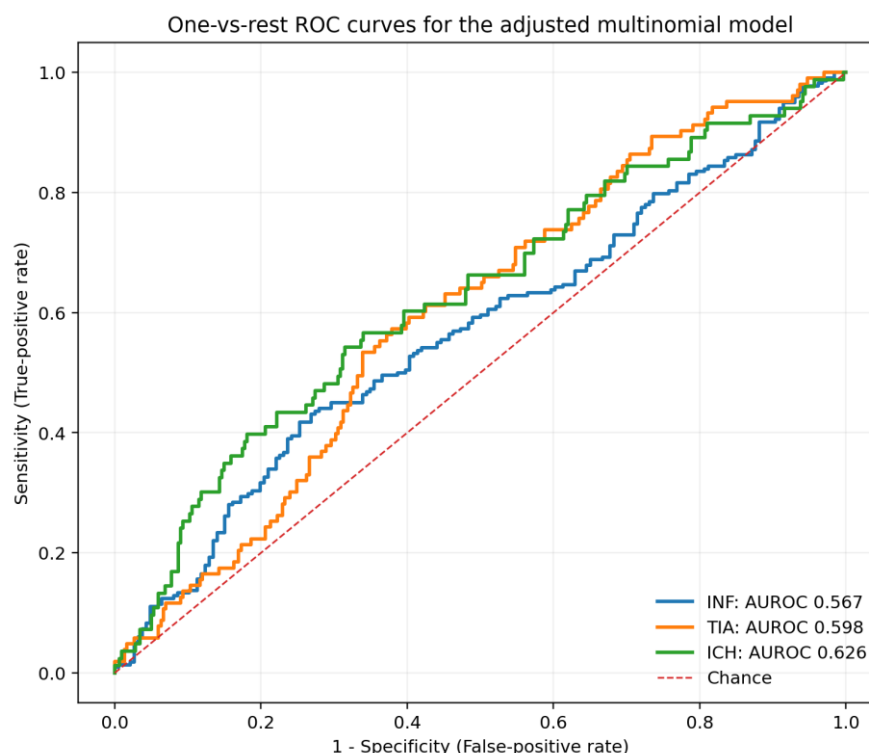


Figure 5. One-vs-rest ROC curves from the adjusted multinomial model (N=404). The diagonal line represents chance discrimination.

9.1 Internal cross-validation of discrimination

Method. To examine whether the apparent AUROC was optimistic, a stratified 10-fold cross-validation was also performed. In each

fold, the multinomial model was refitted on the training portion and probabilities were generated for patients held out from model fitting. Cross-validated discrimination estimates are summarized in Table 10.

Table 10. Ten-fold cross-validated one-vs-rest AUROC performance of the adjusted multinomial model.

Contrast	10-fold cross-validated AUROC	Interpretation
INF vs rest	0.442	No reliable held-out discrimination
TIA vs rest	0.491	No reliable held-out discrimination
ICH vs rest	0.521	No reliable held-out discrimination
Macro-average	0.485	No reliable held-out discrimination
Weighted-average	0.471	No reliable held-out discrimination

Interpretation. The cross-validated macro AUROC was 0.485, with class-specific values near chance. The reduction from the apparent AUROC indicates that the already modest in-sample discrimination does not generalize well within internal resampling. This supports presenting the regression chiefly as an association analysis rather than as a clinical prediction tool. The class-specific cross-validated estimates are shown in Table 10.

9.2 Incremental discrimination contributed by cIMT

Research question. Even if cIMT is not independently significant, does adding it to conventional clinical covariates improve the ability to distinguish ischemic presentation (INF+TIA) from ICH? The incremental discrimination analysis is summarized in Table 11.

Table 11. Incremental AUROC for discrimination of ischemic presentation versus intracerebral hemorrhage.

Binary model: ischemic vs ICH	AUROC	95% CI	Comment
Mean cIMT alone	0.505	0.431-0.577	Essentially chance discrimination
Clinical covariates only	0.629	0.560-0.696	Modest apparent discrimination
Clinical covariates + mean cIMT	0.626	0.556-0.694	No improvement over clinical model

Incremental AUROC result. The clinical-only model had AUROC 0.629; after adding mean cIMT the AUROC was 0.626. The AUROC change was -0.003 with bootstrap 95% CI -0.016-0.009, which includes zero. Thus the dataset provides no evidence that

mean cIMT adds discriminative information for ischemic versus hemorrhagic presentation beyond the clinical covariates. Comparative AUROC values are provided in Table 11.

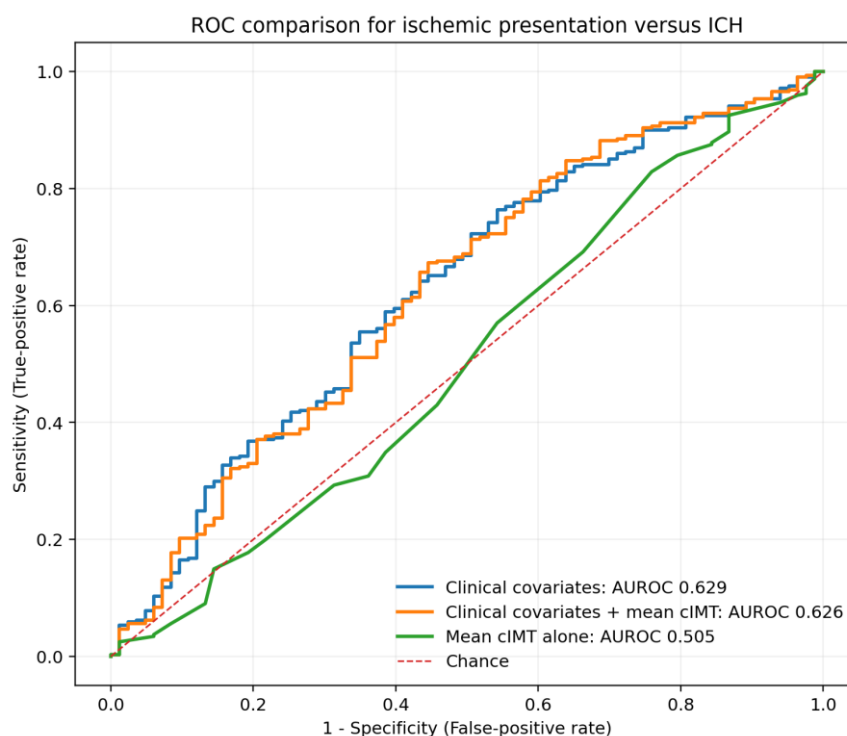


Figure 6. ROC curves for ischemic presentation (INF+TIA) versus ICH. Mean cIMT alone lies close to the chance line; adding cIMT to the clinical covariates does not increase the AUROC.

10. Model diagnostics and data-quality sensitivity analysis

Multicollinearity. The highest VIF in the primary model was 2.18. This is well below commonly used concern thresholds and indicates that the reported cIMT effect is not being masked by severe linear dependence among the covariates. Individual VIF values are listed in Table 12.

Table 12. Variance inflation factors for predictors included in the primary adjusted model.

Predictor	VIF
Age per 10 y	1.09
Male sex	1.37
Hypertension	1.33
Diabetes	2.18
Smoking	1.37
SBP per 10 mmHg	1.34
HbA1c per 1%	2.14
LDL-C per 10 mg/dL	1.22
TG/HDL ratio per 1	1.23
Creatinine per 1 mg/dL	1.07
cIMT per 1 SD	1.09

Very-low-cIMT sensitivity analysis. After excluding the seven records with at least one CCA-IMT <0.30 mm, N=433 remained. The groupwise mean-cIMT comparison remained non-significant ($H=0.516$, $P=0.773$). In the adjusted model, mean cIMT remained non-significant for INF vs ICH (aOR 0.98, 95% CI 0.75-1.28; $P=0.889$) and TIA vs ICH (aOR 0.96, 95% CI 0.71-1.30; $P=0.788$).

Interpretation. The principal cIMT conclusion is robust to exclusion of the physiologically questionable very-low IMT records. The negative cIMT finding is therefore unlikely to be an artifact created by those extreme data points.

11. Integrated interpretation of the complete analysis

The data show a consistent distinction between diffuse carotid wall thickness and focal plaque. Bilateral CCA-IMT, whether represented by the right side, left side, mean, maximum value, or inter-side asymmetry, is nearly identical across INF, TIA, and ICH. This remains true after adjustment for major vascular risk factors, after expressing cIMT

per one SD, after allowing a nonlinear spline function, and after removing very-low cIMT values. AUROC analysis reaches the same conclusion from a different statistical perspective: mean cIMT alone has essentially chance-level discrimination for ischemic versus hemorrhagic presentation and does not improve the AUROC of a model based on conventional clinical covariates.

Plaque presence, in contrast, differs across the three presentation groups, with the strongest difference between INF and TIA. However, plaque laterality and simplified anatomical topography are not statistically different, and plaque presence does not become an independently significant predictor of INF or TIA versus ICH in the fully adjusted sensitivity models. This suggests that focal plaque burden may capture a group-level difference in atherosclerotic phenotype, but the present dataset does not support using plaque or cIMT as a stand-alone classifier of presentation subtype.

For manuscript framing, the strongest result is therefore not that a carotid Doppler measurement predicts a particular event type, but that structural carotid phenotyping reveals different behavior of two related vascular markers: cIMT is a generalized vascular-burden marker associated with plaque presence, whereas focal plaque prevalence varies by presentation, particularly between infarction and TIA. The low internally validated AUROCs should be reported transparently and argue against presenting the model as a clinical diagnostic tool without external validation.

12. Summary of the Results section of the analysis:

Among 443 patients, 238 presented with ischemic infarction, 113 with transient ischemic attack and 92 with intracerebral hemorrhage. CCA-IMT measures were non-normally distributed; therefore group comparisons were performed using Kruskal-Wallis testing. Right CCA-IMT, left CCA-IMT, mean bilateral cIMT, maximum cIMT

and absolute inter-side asymmetry did not differ across INF, TIA and ICH (all $P > 0.50$). Mean bilateral cIMT was 1.10 ± 0.23 mm in INF, 1.09 ± 0.25 mm in TIA and 1.09 ± 0.26 mm in ICH ($H = 0.574$, $P = 0.751$).

Among 374 patients with interpretable plaque coding, plaque was present in 60.6% of INF, 42.6% of TIA and 57.1% of ICH patients ($\chi^2 = 8.585$, $P = 0.014$). After Holm correction, the difference was significant for INF versus TIA (adjusted $P = 0.011$), but not for INF versus ICH or TIA versus ICH. Plaque laterality ($P = 0.055$) and simplified plaque topography ($P = 0.066$) were not significantly different among presentation groups.

In the primary complete-case multinomial logistic regression ($N = 404$; ICH reference), a one-SD increase in mean bilateral cIMT was not independently associated with INF (aOR 1.07, 95% CI 0.82-1.41; $P = 0.607$) or TIA (aOR 1.06, 95% CI 0.78-1.45; $P = 0.705$). The overall multinomial model was not significant (likelihood-ratio $P = 0.617$; McFadden pseudo- $R^2 = 0.024$). Separate models using right, left, mean and maximum cIMT yielded concordant non-significant cIMT effects. Restricted cubic spline analysis showed no evidence of a nonlinear cIMT-presentation association (P for nonlinearity = 0.567).

The adjusted multinomial model showed modest apparent discrimination (macro-average one-vs-rest AUROC 0.597, 95% CI 0.553-0.641), but 10-fold cross-validation reduced the macro AUROC to 0.485. For the binary comparison of ischemic presentation versus ICH, mean cIMT alone had AUROC 0.505; the clinical model had AUROC 0.629, and addition of mean cIMT produced AUROC 0.626, an absolute change of only -0.003 (95% CI -0.016-0.009). These findings indicate no incremental discriminative value of mean cIMT for presentation subtype in this dataset.

Sensitivity models separating cIMT from plaque, the combined cIMT-plus-plaque model, and exclusion of the seven records with very-low cIMT all produced materially

similar results. Mean cIMT was nevertheless independently associated with carotid plaque presence (aOR 1.60 per one-SD increase, 95% CI 1.24-2.07; $P < 0.001$), supporting internal consistency between diffuse carotid wall thickening and focal atherosclerotic plaque.

Important reporting note

The AUROC values in the main table are apparent (in-sample) discrimination estimates from the fitted model and should not be described as externally validated diagnostic accuracy. The 10-fold cross-validated results are included specifically to show the degree of optimism in the apparent fit. If this manuscript is submitted as an association/phenotyping study, the odds ratios, confidence intervals, plaque comparisons and spline analysis should remain the primary results; AUROC should be presented as an exploratory model-performance analysis.

DISCUSSION

Principal findings and overall interpretation

This study compared bilateral common carotid intima-media thickness (CCA-IMT) and plaque patterns in 443 patients with ischemic infarction (INF; $n = 238$), transient ischemic attack (TIA; $n = 113$), and intracerebral hemorrhage (ICH; $n = 92$). Three findings deserve emphasis. First, right, left, mean, maximum, and inter-side asymmetric CCA-IMT measurements were remarkably similar across the three clinical presentations. Mean bilateral cIMT was approximately 1.10 mm in each group, and the overall comparison was non-significant ($H = 0.574$, $P = 0.751$). Second, focal carotid plaque behaved differently from cIMT: among 374 patients with interpretable plaque coding, plaque prevalence was 60.6% in INF, 42.6% in TIA, and 57.1% in ICH ($P = 0.014$), with the most robust pairwise difference between INF and TIA after multiplicity correction. Third, neither cIMT nor plaque provided strong independent discrimination of

presentation subtype after adjustment. A 1-SD increase in mean cIMT was not associated with INF versus ICH (aOR 1.07, 95% CI 0.82-1.41) or TIA versus ICH (aOR 1.06, 95% CI 0.78-1.45), and mean cIMT alone had an AUROC of only 0.505 for ischemic presentation versus ICH. These findings suggest that, among patients with established cerebrovascular disease, cIMT is better interpreted as a marker of generalized vascular burden than as a discriminator of the presenting event.

cIMT across ischemic infarction, TIA and ICH

Several earlier studies reported greater CCA-IMT in ischemic stroke than in ICH. Vemmos et al. found significantly higher CCA-IMT in 126 patients with brain infarction than in 30 patients with ICH; after adjustment, each 0.1-mm increase in CCA-IMT was associated with an odds ratio of 1.29 for infarction versus ICH. [24] Tsigoulis et al., studying hypertensive patients with lacunar infarction and ICH, reported mean CCA-IMT values of 0.926 and 0.815 mm, respectively, and a 36.6% increase in the probability of lacunar infarction versus ICH for each 0.1-mm increment. [14] Moghtaderi et al. likewise observed significant differences in CCA-IMT among large-vessel ischemic, small-vessel ischemic, and hemorrhagic stroke groups. [13] At first sight, these reports contrast with our essentially identical median cIMT of 1.10 mm across INF, TIA, and ICH.

The difference is biologically plausible and may reflect study design rather than a true contradiction. Our ischemic category is broader than lacunar-only or etiologically separated ischemic cohorts, and our ICH patients also showed a high burden of carotid disease. Prospective data also show that cIMT is not exclusive to atherosclerotic infarction. In the ARIC study, Ohira et al. found increasing stroke incidence across higher IMT levels for hemorrhagic, lacunar, non-lacunar, and cardioembolic stroke; the strongest adjusted associations were for non-

lacunar and cardioembolic events, but hemorrhagic stroke also rose with higher IMT. [11] Folsom et al., combining ARIC and Cardiovascular Health Study data, showed that greater carotid IMT was independently associated with incident ICH, with the highest IMT quartile carrying approximately 2.5- to 3.7-fold higher ICH risk than the lowest quartile. [15] These observations support carotid wall thickening as a marker of cumulative hypertensive and systemic vascular injury as well as atherosclerosis, helping explain the high cIMT observed in our ICH group.

The systematic review by Kumar et al. is informative. Across 19 studies, increased CCA-IMT was strongly associated with ischemic stroke versus controls, and pooled data suggested greater cIMT in ischemic stroke than ICH, but substantial variation existed across stroke subtypes and study populations. [16] Thus, our findings do not negate the epidemiological association between cIMT and stroke; they indicate that cIMT may have limited ability to distinguish infarction, transient ischemia, and hemorrhage once cerebrovascular disease is clinically manifest.

Plaque prevalence: a stronger phenotypic signal than cIMT

The clearest structural difference in our study was plaque prevalence. Plaque was present in 60.6% of INF compared with 42.6% of TIA, while the ICH prevalence was also substantial at 57.1%. The INF-versus-TIA difference suggests greater focal carotid atherosclerotic burden in completed infarction, although causality cannot be inferred. Iannuzzi et al., in 242 stroke and 336 TIA patients, demonstrated that carotid plaque characteristics were closely related to ischemic events: stroke was associated with ipsilateral carotid occlusion and a narrower residual lumen, whereas TIA was associated with hypoechoic plaques and longitudinal plaque motion; plaque thickness was greater on the symptomatic side in both groups. [17] Although our dataset lacks plaque

echogenicity, ulceration, mobility, and stenosis severity, the higher plaque frequency in INF is directionally consistent with greater focal atherosclerotic burden.

Large population studies similarly suggest that plaque can contain information not captured by cIMT. In the Tromsø Study, Mathiesen et al. followed 6,584 participants for approximately 10 years and found that total plaque area predicted first-ever ischemic stroke in both sexes; plaque area was a stronger predictor than IMT, and the highest plaque-area quartile conferred adjusted hazard ratios of 1.73 in men and 1.62 in women compared with no plaque. [10] In the Rotterdam Study, Hollander et al. reported that carotid plaques increased stroke and cerebral-infarction risk by about 1.5-fold, with severe plaque burden particularly associated with anterior-circulation and lacunar infarction. [12] These observations parallel our finding that plaque prevalence separated groups when cIMT did not.

Nevertheless, plaque topography and laterality were not significant in our study ($P=0.066$ and $P=0.055$, respectively). This is plausible. Hollander et al. found increased stroke risk largely irrespective of plaque location, supporting the interpretation that carotid plaque can function both as a local embolic source and as a marker of generalized atherosclerosis. [12] Similarly, Yoon et al. found no significant difference in plaque presence, site, or size between large-territory and small-vessel ischemic stroke despite significantly thicker cIMT in large-territory infarction. [25] Simple anatomic location may therefore be less informative than plaque burden or vulnerability. Future studies incorporating plaque thickness, surface irregularity, echolucency, calcification, stenosis percentage, and plaque volume may provide greater resolution.

Why cIMT did not independently classify presentation

Our adjusted models reinforce the unadjusted findings. Right, left, mean, and maximum cIMT all produced non-significant adjusted

effects, and restricted cubic spline analysis showed no evidence of a nonlinear threshold or U-shaped relationship (P for nonlinearity=0.567). This indicates that the negative result is unlikely to reflect selection of the wrong cIMT summary or an inappropriate linear assumption. Nagai et al. previously compared bilateral mean IMT with a carotid plaque score in 311 stroke patients and 792 nonstroke subjects. Both measures were useful for atherothrombotic and lacunar infarction, but plaque score discriminated atherothrombotic infarction better than IMT (AUROC 0.80 versus 0.68). [19] Our AUROC of 0.505 addresses a harder question: discrimination among established cerebrovascular presentations rather than stroke versus nonstroke controls. This different target population likely explains much of the lower performance.

Ravikanth et al. also reported higher mean cIMT in 500 acute ischemic infarction cases than in 250 healthy controls (approximately 0.912 versus 0.794 mm) and observed increasing cIMT across plaque-stenosis categories. [21] Such case-control separation does not imply that cIMT can identify stroke subtype among symptomatic patients. Shimoda et al. found that the highest quartile of maximum CCA-IMT was associated more strongly with ischemic and lacunar stroke than hemorrhagic stroke, but their cohort assessed future events in initially cardiovascular-disease-free participants. [20] The contrast highlights the distinction between etiologic risk prediction and diagnostic discrimination at presentation.

AUROC and incremental predictive value

Model performance should be interpreted conservatively. The apparent macro-average AUROC of the multinomial model was 0.597, but 10-fold cross-validation reduced it to 0.485, indicating substantial optimism and no reliable held-out discrimination. For ischemic presentation versus ICH, the clinical model achieved an apparent AUROC of 0.629; adding mean cIMT produced an AUROC of 0.626, an absolute change of -

0.003. This absence of incremental discrimination is consistent with broader cardiovascular literature. In an individual-participant meta-analysis of 45,828 participants, Den Ruijter et al. found that adding common cIMT to the Framingham risk model changed the C statistic only from 0.757 to 0.759 and yielded a small net reclassification improvement of 0.8%.^[8] Prati et al. likewise found that cIMT >1 mm and carotid plaque predicted ischemic cerebrovascular events over 12.7 years, but adding carotid findings improved prediction beyond the Framingham Stroke Risk Score mainly in subjects already at high baseline risk.^[26] Our AUROC results therefore fit a recurring theme: cIMT can be associated with vascular events without adding substantial individual-level classification

once conventional risk factors or overt vascular disease are present.

An additional internally coherent finding was that mean cIMT strongly predicted plaque presence (aOR 1.60 per 1-SD increase, 95% CI 1.24-2.07; $P < 0.001$). This supports internal biological consistency. cIMT and plaque are related manifestations of vascular remodeling, yet they are not interchangeable. cIMT partly reflects age- and pressure-related medial hypertrophy, whereas plaque represents focal intimal atherosclerosis. Low VIF values also indicate that the null subtype associations were not explained by problematic collinearity.

Comparative Summary of 15 Closely Related Studies (Table 13)

Table 13. Comparative summary of 15 closely related published studies and their relation to the present findings.

Study	Key published finding	Comparison with present study
Vemmos et al., 2004 ^[24]	BI n=126 vs ICH n=30; CCA-IMT higher in BI; adjusted OR 1.29 per 0.1 mm.	Present study: mean cIMT ~1.10 mm in all groups; no INF-vs-ICH association after adjustment.
Tsivgoulis et al., 2005 ^[14]	Hypertensive LI n=92 vs ICH n=67; CCA-IMT 0.926 vs 0.815 mm; 36.6% higher LI odds per 0.1 mm.	Present study did not reproduce cIMT discrimination, probably reflecting broader INF phenotyping and high vascular burden in ICH.
Moghtaderi et al., 2014 ^[13]	Significant CCA-IMT differences among large-vessel, small-vessel and hemorrhagic stroke groups.	Our broader INF/TIA/ICH comparison showed extensive cIMT overlap.
Ohira et al., 2011 (ARIC) ^[11]	Higher IMT associated with hemorrhagic, lacunar, nonlacunar and cardioembolic stroke; strongest for nonlacunar/cardioembolic events.	Supports cIMT as a generalized vascular marker and helps explain substantial cIMT in ICH.
Folsom et al., 2011 ^[15]	Higher carotid IMT independently predicted incident ICH; highest quartile had about 2.5-3.7-fold higher risk.	Consistent with our finding that ICH patients also had high cIMT.
Kumar et al., 2020 ^[16]	Meta-analysis: ischemic stroke cIMT greater than controls and, overall, greater than ICH; heterogeneity across subtypes.	Our null between-presentation result adds evidence that cIMT may not distinguish all symptomatic populations.
Iannuzzi et al., 1995 ^[17]	Stroke/TIA linked to plaque features; stroke with occlusion/narrow lumen, TIA with hypoechoic/mobile plaques; plaque thickness higher ipsilaterally.	Our plaque prevalence was higher in INF than TIA, but morphology/stenosis were unavailable.
Mathiesen et al., 2011 ^[10]	Total plaque area predicted first-ever ischemic stroke and was generally stronger than IMT.	Strongly parallels our plaque signal despite absent cIMT group separation.
Hollander et al., 2002 ^[12]	Plaques increased stroke/infarction risk about 1.5-fold; risk often independent of plaque location.	Supports our significant plaque-presence result but non-significant topography result.
Yoon et al., 2010 ^[25]	Large-territory stroke had thicker cIMT than small-vessel stroke, while plaque presence/site/size did not differ.	Shows that cIMT and plaque topography can behave differently across stroke phenotypes.

Study	Key published finding	Comparison with present study
Nagai et al., 2002 ^[19]	Plaque score AUROC 0.80 vs IMT AUROC 0.68 for atherothrombotic infarction vs nonstroke.	Our mean-cIMT AUROC 0.505 reflects the harder task of classifying among symptomatic cerebrovascular groups.
Ravikanth, 2020 ^[21]	Ischemic cases had higher cIMT than healthy controls (0.912 vs 0.794 mm) and cIMT rose with plaque stenosis.	Supports cIMT as disease-burden marker, but not necessarily as an event-subtype discriminator.
Shimoda et al., 2020 ^[20]	Highest maximum CCA-IMT quartile associated more strongly with ischemic/lacunar than hemorrhagic stroke in prospective follow-up.	Different from our cross-sectional subtype discrimination; reinforces distinction between risk prediction and presentation classification.
Den Ruijter et al., 2012 ^[8]	Adding common cIMT to Framingham changed C statistic only 0.757 to 0.759; NRI 0.8%.	Closely matches our finding that cIMT did not improve AUROC beyond clinical covariates.
Prati et al., 2008 ^[26]	cIMT >1 mm and plaque predicted ischemic events, but incremental prediction was limited except in high-risk subjects.	Consistent with high cIMT as a vascular-risk marker but weak incremental subtype classification in our cohort.

Strengths And Limitations

This study drew strength from the direct comparison of three clinically important cerebrovascular presentations within one hospital cohort. Bilateral carotid measurements allowed investigators to examine side-specific values, overall wall thickness, and asymmetry instead of relying on a single cIMT measurement. Separate assessment of plaque presence and anatomical distribution captured focal disease that could have been missed by a wall-thickness-only approach. Adjusted regression, nonlinear modelling, missing-data-aware subgroup analyses, and cross-validation provided complementary checks on the consistency and practical discriminative value of the findings.

The study had important limitations. Its single-centre observational design and absence of a neurologically unaffected control group restricted causal interpretation and external generalizability. The study period, recruitment sequence, diagnostic adjudication details, imaging protocol, and Doppler measurement reproducibility were not specified in the available manuscript. Plaque codes could be interpreted for only 374 of 443 patients; a further reduction to 404 complete cases for the primary model raised the possibility of missing-data bias. Carotid plaque morphology, stenosis severity, ulceration, and echogenicity were not captured, and infarction mechanisms

were not separated into etiologic subtypes. A small number of implausibly low cIMT recordings prompted sensitivity analyses. Finally, weak cross-validated discrimination indicated that these findings should not be used as a clinical classification tool without independent validation.

CONCLUSION

In this hospital-based cohort of 443 patients with ischemic infarction, transient ischemic attack, or intracerebral hemorrhage, bilateral common carotid intima-media thickness and its derived measures overlapped substantially between clinical groups and did not independently discriminate cerebrovascular presentation. In contrast, focal carotid plaque was more frequent among patients with infarction than among those with TIA, although plaque laterality and simplified anatomical topography were not significantly different. Greater cIMT remained associated with the presence of plaque, supporting its value as a marker of carotid vascular burden rather than as a stand-alone test for classifying the type of acute cerebrovascular event. The poor performance on internal cross-validation further discouraged diagnostic use of the model. Larger multicentre studies with standardized carotid imaging, detailed plaque characterization, and better-defined ischemic stroke mechanisms were warranted to establish whether integrated carotid

phenotyping could offer clinically useful additional information.

Declaration

Acknowledgement: None

Source of Funding: None

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

Creative Commons Attribution License 4.0

This is an open-access article published under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0).

<https://creativecommons.org/licenses/by/4.0>

REFERENCES

1. GBD 2021 Stroke Risk Factor Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Neurol.* 2024;23(10):973-1003. doi:10.1016/S1474-4422(24)00369-7.
2. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockcroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: a guideline from the American Heart Association/American Stroke Association. *Stroke.* 2021;52(7):e364-e467. doi:10.1161/STR.0000000000000375.
3. Greenberg SM, Ziai WC, Cordonnier C, Dowlatshahi D, Francis B, Goldstein JN, et al. 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: a guideline from the American Heart Association/American Stroke Association. *Stroke.* 2022;53(7):e282-e361. doi:10.1161/STR.0000000000000407.
4. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Desvarieux M, et al. Mannheim intima-media thickness consensus. *Cerebrovasc Dis.* 2004;18(4):346-349. doi:10.1159/000081812.
5. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. *J Am Soc Echocardiogr.* 2008;21(2):93-111. doi: 10.1016/j.echo.2007.11.011.
6. Howard G, Sharrett AR, Heiss G, Evans GW, Chambless LE, Riley WA, et al. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound: ARIC Investigators. *Stroke.* 1993;24(9):1297-1304. doi: 10.1161/01.STR.24.9.1297.
7. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. *N Engl J Med.* 2011;365(3):213-221. doi:10.1056/NEJMoa1012592.
8. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA.* 2012;308(8):796-803. doi:10.1001/jama.2012.9630.
9. Tschiderer L, Seekircher L, Izzo R, Mancusi C, Manzi MV, Baldassarre D, et al. Association of intima-media thickness measured at the common carotid artery with incident carotid plaque: individual participant data meta-analysis of 20 prospective studies. *J Am Heart Assoc.* 2023;12(12):e027657. doi:10.1161/JAHA.122.027657.
10. Mathiesen EB, Johnsen SH, Wilsgaard T, Bønaa KH, Løchen ML, Njølstad I. Carotid plaque area and intima-media thickness in prediction of first-ever ischemic stroke: a 10-year follow-up of 6584 men and women: the Tromsø Study. *Stroke.* 2011;42(4):972-978. doi:10.1161/STROKEAHA.110.589754.
11. Ohira T, Shahar E, Iso H, Chambless LE, Rosamond WD, Sharrett AR, et al. Carotid artery wall thickness and risk of stroke subtypes: the Atherosclerosis Risk in Communities Study. *Stroke.* 2011;42(2):397-403. doi:10.1161/STROKEAHA.110.592261.
12. Hollander M, Bots ML, Del Sol AI, Koudstaal PJ, Witteman JC, Grobbee DE, et al. Carotid plaques increase the risk of stroke and subtypes of cerebral infarction in asymptomatic elderly: the Rotterdam Study. *Circulation.* 2002;105(24):2872-2877. doi: 10.1161/01.CIR.0000018650.58984.75.
13. Moghtaderi A, Sanei-Sistani S, Abdollahi G, Dahmardeh H. Comparison of intima-media

- thickness of common and internal carotid arteries of patients with ischemic stroke and intracerebral hemorrhage. *Iran J Neurol.* 2014;13(4):226-230.
14. Tsivgoulis G, Vemmos KN, Spengos K, Papamichael CM, Cimboneriu A, Zis V, et al. Common carotid artery intima-media thickness for the risk assessment of lacunar infarction versus intracerebral haemorrhage. *J Neurol.* 2005;252(9):1093-1100. doi:10.1007/s00415-005-0821-0.
 15. Folsom AR, Yatsuya H, Psaty BM, Shahar E, Longstreth WT Jr. Carotid intima-media thickness, electrocardiographic left ventricular hypertrophy, and incidence of intracerebral hemorrhage. *Stroke.* 2011;42(11):3075-3079. doi:10.1161/STROKEAHA.111.623157.
 16. Kumar P, Sharma R, Misra S, Kumar A, Nath M, Nair P, et al. CIMT as a risk factor for stroke subtype: a systematic review. *Eur J Clin Invest.* 2020;50(11): e13348. doi:10.1111/eci.13348.
 17. Iannuzzi A, Wilcosky T, Mercuri M, Rubba P, Bryan FA, Bond MG. Ultrasonographic correlates of carotid atherosclerosis in transient ischemic attack and stroke. *Stroke.* 1995;26(4):614-619. doi: 10.1161/01.STR.26.4.614.
 18. Lu M, Zhang L, Yuan F, Peng P, Zhang H, Liu S, et al. Comparison of carotid atherosclerotic plaque characteristics between symptomatic patients with transient ischemic attack and stroke using high-resolution magnetic resonance imaging. *BMC Cardiovasc Disord.* 2022; 22:190. doi:10.1186/s12872-022-02624-7.
 19. Nagai Y, Kitagawa K, Yamagami H, Kondo K, Hougaku H, Hori M, et al. Carotid artery intima-media thickness and plaque score for the risk assessment of stroke subtypes. *Ultrasound Med Biol.* 2002;28(10):1239-1243. doi:10.1016/S0301-5629(02)00573-2.
 20. Shimoda S, Kitamura A, Imano H, Cui R, Muraki I, Yamagishi K, et al. Associations of carotid intima-media thickness and plaque heterogeneity with the risks of stroke subtypes and coronary artery disease in the Japanese general population: the Circulatory Risk in Communities Study. *J Am Heart Assoc.* 2020;9(19): e017020. doi:10.1161/JAHA.120.017020.
 21. Ravikanth R. Relevance of carotid intima-media thickness and plaque morphology in the risk assessment of patients with acute ischemic cerebral infarcts: a case-control study of large series from a single center. *J Med Ultrasound.* 2020;28(1):29-34. doi: 10.4103/JMU.JMU_5_19.
 22. Herder M, Johnsen SH, Arntzen KA, Mathiesen EB. Risk factors for progression of carotid intima-media thickness and total plaque area: a 13-year follow-up study: the Tromsø Study. *Stroke.* 2012;43(7):1818-1823. doi:10.1161/STROKEAHA.111.646596.
 23. Yilmaz MI, Qureshi AR, Carrero JJ, Saglam M, Suliman ME, Caglar K, et al. Predictors of carotid artery intima-media thickness in chronic kidney disease and kidney transplant patients without overt cardiovascular disease. *Am J Nephrol.* 2010;31(3):214-221. doi:10.1159/000272936.
 24. Vemmos KN, Tsivgoulis G, Spengos K, Papamichael CM, Zakopoulos N, Daffertshofer M, et al. Common carotid artery intima-media thickness in patients with brain infarction and intracerebral haemorrhage. *Cerebrovasc Dis.* 2004;17(4):280-286. doi:10.1159/000077338.
 25. Yoon HJ, Jeong MH, Kim KH, Ahn Y, Cho JG, Park JC, et al. Carotid intima-media thickness, not carotid plaque, is associated with large territory cerebral infarction in patients with ischemic stroke. *Korean Circ J.* 2010;40(6):272-276. doi:10.4070/kcj.2010.40.6.272.
 26. Prati P, Tosoletto A, Vanuzzo D, Bader G, Casaroli M, Canciani L, et al. Carotid intima-media thickness and plaques can predict the occurrence of ischemic cerebrovascular events. *Stroke.* 2008;39(9):2470-2476. doi:10.1161/STROKEAHA.107.511584.
- How to cite this article: Saha AK, Chatterjee P, Mukherjee M. Bilateral common carotid intima-media thickness and plaque topography across ischemic infarction, transient ischemic attack, and intracerebral hemorrhage: a multivariable carotid phenotyping study. *Int J Health Sci Res.* 2026; 16(10):105-127. doi: 10.52403/ijhsr.20261012
