CLINICAL AND INSTRUMENTAL CHARACTERISTICS OF PATIENTS WITH ISCHEMIC STROKE AND STENOTIC AND NON-STENOTIC EXTRACRANIAL ATHEROSCLEROSIS

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ABSTRACT

Background. Non-stenotic extracranial atherosclerosis is increasingly regarded as a clinically relevant source of ischemic stroke, particularly when plaque vulnerability is present despite the absence of severe luminal narrowing.

Aim. To compare computed tomography, computed tomographic angiography, magnetic resonance imaging, ultrasonographic and integrated clinical-instrumental characteristics in ischemic stroke patients with stenotic and non-stenotic extracranial atherosclerosis.

Materials and Methods. The clinical observational comparative study with a cross-sectional analytical framework and retrospective and prospective components included 100 patients with verified non-lacunar ischemic stroke and ipsilateral extracranial atherosclerosis: 50 with stenotic (≥50% luminal narrowing of the culprit ipsilateral extracranial artery) and 50 with non-stenotic disease (<50%). MRI variables (median [Q1; Q3] for quantitative, n (%) for categorical) were analyzed using Shapiro–Wilk (normality), Mann–Whitney U, chi-square or Fisher's exact (group comparisons), and Spearman's correlation. Statistical analysis was performed using Statistica 8.0 (StatSoft, USA). The study was conducted as an aspect of the author's dissertation and research project "Anatomical-functional and neurohumoral features of neurological consequences of traumatic and vascular injuries of the nervous system in different age periods" (state registration number 0121U000035).

Research Ethics. The study complied with medical research ethics standards of the World Medical Association Declaration of Helsinki (1964–2024). Written informed consent for examination, treatment and use of anonymized clinical data for research purposes was obtained from all participants or their legal representatives.

Results. Stenotic atherosclerosis was associated with lower ASPECTS (Alberta Stroke Program Early CT Score) (8.0 [7.0; 8.8] versus 9.0 [8.0; 9.0]; p<0.001), larger infarct volume (47.9 [35.8; 55.8] ml versus 33.2 [23.6; 39.2] ml; p<0.001), greater culprit stenosis and higher ipsilateral internal carotid artery flow velocities. Non-stenotic disease showed more frequent vulnerability markers: lower plaque gray-scale median, higher vulnerability score and high vulnerability in 64.0% versus 20.0% of patients (p<0.001). Early neurological deterioration was also more frequent in the non-stenotic group (30.0% versus 8.0%; p=0.005).

Conclusions. Stenotic disease formed a hemodynamic and large-infarct phenotype, whereas non-stenotic disease formed a vulnerability-driven phenotype requiring plaque-oriented risk stratification.

Keywords: *endocrinology, literature review, deiodinases, thyroid hormones, energy metabolism, cytokines*.

Abbreviations

ADC – Apparent Diffusion Coefficient;

ASPECTS – Alberta Stroke Program Early CT Score;

CTA – Computed Tomographic Angiography;

DWI – Diffusion-Weighted Imaging;

EDV – End-Diastolic Velocity;

ESUS – Embolic Stroke of Undetermined Source;

FLAIR – Fluid-Attenuated Inversion Recovery;

GSM – Gray-Scale Median;

HR-VWI – High-Resolution Vessel Wall Imaging;

ICA – Internal Carotid Artery;

LRNC – Lipid-Rich Necrotic Core;

MRI – Magnetic Resonance Imaging;

NASCET – North American Symptomatic Carotid Endarterectomy Trial;

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NIHSS – National Institutes of Health Stroke Scale;

PI – Pulsatility Index;

PSV – Peak Systolic Velocity;

RI – Resistance Index;

TCD – TransCranial Doppler ultrasonography;

TOAST – Trial of Org 10172 in Acute Stroke Treatment Classification.

Introduction

Secondary prevention after ischemic stroke requires determining the most probable stroke mechanism and differentiation between large-artery atherosclerotic, cardioembolic, small-vessel, and other etiological categories. Contemporary recommendations emphasize individualized vascular risk reduction and causal diagnosis rather than uniform post-stroke management [1]. The TOAST classification remains a practical etiological framework, but it is limited when the patient has an ipsilateral carotid plaque causing less than 50% stenosis [2].

For symptomatic extracranial carotid disease, clinical decision-making has traditionally been stenosis-centred. European and vascular-surgical guidelines use the degree of luminal narrowing and symptom status as major criteria for carotid revascularization [3; 4]. This paradigm is appropriate for severe stenosis, but it does not fully describe the biological activity of atherosclerotic plaque. Non-stenotic plaques can have a large lipid-rich necrotic core, intraplaque hemorrhage, surface ulceration, hypodensity, neovascularization or a thin fibrous cap; each of these features may increase the risk of artery-to-artery embolism even when flow-limiting stenosis is absent [5; 6].

Computed tomography and computed tomographic angiography are widely available in acute stroke pathways and provide early information on ischemic injury, large-vessel occlusion, collateral status and luminal stenosis. Magnetic resonance imaging can confirm acute ischemia, characterize infarct pattern and estimate lesion burden. Duplex ultrasonography and Doppler-derived indices add functional information on flow acceleration, resistance, pulsatility and plaque echogenicity. Therefore, a multimodal instrumental approach may clarify whether a patient belongs predominantly to a hemodynamic-stenotic phenotype or to a morphologically vulnerable plaque phenotype [6–8].

The contradiction addressed in this study is clinically important: stenotic atherosclerosis is readily recognized as high-risk, whereas non-stenotic extracranial atherosclerosis may be underestimated despite features of vulnerability. Resolving this contradiction is relevant for optimization of preventive strategies and for early prediction of atherosclerosis progression in patients with ischemic stroke.

Aim and Objectives

The ***aim*** of the study was to optimize preventive risk stratification and prognostic assessment of atherosclerosis progression in patients with ischemic stroke and stenotic or non-stenotic atherosclerosis of the extracranial cerebral arteries by analysing instrumental markers of vascular lesion severity, plaque morphology and ischemic brain injury.

The ***objectives*** were:

1) to compare computed tomography and computed tomographic angiography characteristics in the two groups;

2) to compare magnetic resonance imaging characteristics and infarct patterns;

3) to assess duplex ultrasonography and available transcranial Doppler-derived hemodynamic indicators;

4) to perform an integrated clinical-instrumental analysis of stroke severity, functional outcome, luminal stenosis and plaque vulnerability.

Materials and Methods

A clinical observational comparative study with a cross-sectional analytical framework, incorporating both retrospective and prospective components, was conducted. The retrospective component consisted of extraction of anamnestic, clinical, neuroimaging, ultrasonographic and laboratory data from medical records of patients hospitalized with ischemic stroke. The prospective component included standardized clinical-neurological examination, venous blood sampling for routine laboratory parameters and additional research biomarkers, and unified assessment of ultrasonographic signs of extracranial cerebral artery atherosclerosis.

The study included 100 patients with ischemic stroke (50 patients with stenotic and 50 patients with non-stenotic atherosclerosis of extracranial arteries) and 20 clinically healthy persons. Group assignment was based on the culprit ipsilateral extracranial artery, defined as the artery ipsilateral to the ischemic lesion and carrying the most clinically relevant atherosclerotic lesion. Non-stenotic atherosclerosis was defined as <50% luminal narrowing of the culprit artery. Stenotic atherosclerosis was defined as ≥50% luminal narrowing or occlusion; in the present cohort, all stenotic cases had ≥70% stenosis or occlusion. CTA stenosis

was assessed using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) approach:

Stenosis manifestation (%) =
= [1 − Minimal residual luminal diameter (mm) / / Distal normal internal carotid artery diameter (mm)] × 100 (1).

Duplex ultrasonographic stenosis categories were assigned according to the local vascular ultrasound protocol using luminal narrowing and Doppler velocity criteria.

The study was conducted in 2020–2026 at the clinical bases of the Department of Neurology and Pediatric Neurology of Kharkiv National Medical University: Municipal Non-Profit Enterprise "City Multidisciplinary Hospital No.18" of Kharkiv City Council, Municipal Non-Profit Enterprise of Kharkiv Regional Council "Regional Clinical Hospital", and Private Enterprise "LORITOM Medical Diagnostic Centre".

Inclusion criteria were verified non-lacunar ischemic stroke; ipsilateral extracranial atherosclerotic lesion; availability of clinical, neuroimaging and ultrasonographic data sufficient for group classification; and written informed consent. Exclusion/non-inclusion criteria were atrial fibrillation or another probable cardioembolic source according to TOAST-based etiological assessment, severe renal or hepatic failure, active systemic inflammatory disease, rheumatic disease, acute myocardial infarction, valvular heart disease, prosthetic heart valves, severe heart failure, and other conditions that could substantially affect biomarker levels or distort pathogenetic interpretation.

Early neurological deterioration was defined as an increase in the National Institutes of Health Stroke Scale (NIHSS) score by ≥2 points from baseline or the appearance of a new focal neurological deficit within the first 72 hours after admission, not explained by sedation, metabolic disturbance or intercurrent non-neurological complications.

The instrumental block included non-contrast computed tomography, computed tomographic angiography when performed, magnetic resonance imaging of the brain, duplex ultrasonography of extracranial arteries and available Doppler-derived hemodynamic indices. Non-contrast computed tomography was used to exclude intracranial hemorrhage and assess early ischemic changes with ASPECTS. ASPECTS ranges from 0 to 10 points; lower values indicate a larger extent of early ischemic change in the middle cerebral artery territory [9]. Computed tomographic angiography was analyzed for NASCET-type stenosis, large-vessel occlusion, collateral status and plaque features such as low attenuation, rim sign, intraluminal thrombus and ulceration. Somatom go.Top (Siemens, Germany) and TSX-101A/RC AQUILION RXL (Toshiba, Japan) were used for computed tomography.

Magnetic resonance imaging was analyzed for DWI positivity, ADC restriction, FLAIR positivety, DWI/FLAIR mismatch, microbleeds on susceptibility-weighted imaging, Fazekas score, ischemic lesion volume, vascular territory, infarct pattern and hemorrhagic transformation. Magnetom Avanto, Magnetom C (Siemens, Germany), Achieva 3.0T (Philips, USA) were used for MRI.

Duplex ultrasonography was used to assess the degree and category of stenosis, intima-media thickness, ipsilateral ICA PSV and EDV, ICA/CCA PSV ratio, RI, PI, plaque size, plaque surface, echogenicity, calcification, GSM, neovascularization, intraplaque hemorrhage, lipid-rich necrotic core and fibrous-cap status. Versana Premier (General Electric, USA) ultrasound scanner was used.

Non-contrast CT was performed in all patients as part of the acute diagnostic pathway. MRI was performed when clinically feasible and available. MRI-specific variables were analyzed using complete-case analysis among patients who underwent MRI; no imputation was performed for MRI-derived variables. In the stenotic group, MRI was available in 29 of 50 patients, whereas 21 patients did not undergo MRI. Reasons for non-performance of MRI were contraindications, clinical instability, logistical unavailability, patient refusal, CT-based diagnostic sufficiency. Because MRI availability was unequal between groups, MRI-derived comparisons were considered exploratory and were addressed in the limitations.

CT, CTA, MRI and ultrasonographic findings were interpreted by certified radiologists/ultrasound specialists as part of routine clinical care. Formal blinded central imaging adjudication was not performed. The exact day of MRI after stroke onset was not systematically coded in the analytical database. This was added to the limitations.

Normality of quantitative variables was assessed using the Shapiro–Wilk test. Variables with non-normal distribution are presented as median [Q1; Q3]. Between-group comparisons of continuous variables were performed using the Mann–Whitney U test. Categorical variables were com-

pared using Pearson chi-square test or Fisher exact test, as appropriate. Correlations were evaluated using Spearman rank correlation coefficients. For series of related exploratory comparisons, Bonferroni-adjusted thresholds were additionally considered and explicitly reported. Statistical significance was set at $p<0.05$. Data were managed in Excel 2021 (Microsoft, USA); statistical analysis was performed using Statistica 8.0 (StatSoft, USA).

Research Ethics

The study was conducted in accordance with ethical principles for medical research involving human participants, including the World Medical Association Declaration of Helsinki (1964–2024) and national requirements for clinical research. Written informed consent for examination, treatment and use of anonymized clinical data was obtained from participants or their legal representatives. Resolution of the Bioethics Committee of the Kharkiv Medical Academy of Postgraduate Education was obtained (Protocol No.1 dated February 18, 2020).

Results

Baseline clinical and demographic characteristics of the study groups was performed (*Table 1*).

Quantitative variables are presented as median [Q1; Q3] and were compared using the Mann–Whitney U test. Categorical variables are presented as n (%) and were compared using Pearson chi-square test or Fisher exact test, as appropriate.

Computed tomography and computed tomographic angiography findings

Non-contrast computed tomography of the brain was performed in all patients in both groups and excluded intracranial hemorrhage in 100% of cases. The frequency of early ischemic changes was similar: 64.0% in the stenotic group and 62.0% in the non-stenotic group. However, the quantitative ASPECTS profile differed significantly. Patients with stenotic atherosclerosis had lower ASPECTS, indicating a larger early ischemic burden.

Computed tomographic angiography was performed in 78.0% of patients with stenotic disease and 66.0% with non-stenotic disease. The expected difference in culprit stenosis was confirmed. Good collateral status and low-attenuation plaque were nominally more frequent in the non-stenotic group; however, because of the limited CTA sample size and multiple CTA-derived comparisons, these findings should be regarded as exploratory and hypothesis-generating. Thus, the non-stenotic phenotype was not instrumentally inert; it showed CTA markers compatible with a lipid-rich, potentially vulnerable plaque (*Table 2*).

CTA-derived plaque comparisons were exploratory because CTA was performed in 39 patients in the stenotic group and 33 patients in the non-stenotic group. For the seven CTA-derived comparisons, the Bonferroni-adjusted exploratory threshold would be $p<0.0071$. Therefore, nominal

Table 1. Baseline clinical and demographic characteristics of the study groups

Indicator	Stenotic atherosclerosis (n=50)	Non-stenotic atherosclerosis (n=50)	p
Age, years, median [Q1; Q3]	66.0 [62.2; 69.8]	65.5 [59.0; 70.0]	0.332
Male sex, n (%)	32 (64.0%)	29 (58.0%)	0.539
Body mass index, kg/m²	29.8 [26.8; 32.0]	29.4 [27.2; 32.4]	0.874
Arterial hypertension, n (%)	48 (96.0%)	36 (72.0%)	0.002
Type 2 diabetes mellitus, n (%)	21 (42.0%)	16 (32.0%)	0.300
Coronary artery disease, n (%)	15 (30.0%)	11 (22.0%)	0.362
Current smoking, n (%)	17 (34.0%)	20 (40.0%)	0.534
Prior TIA, n (%)	2 (4.0%)	5 (10.0%)	0.436
Prior ischemic stroke, n (%)	16 (32.0%)	16 (32.0%)	1.000
Prestroke statin use, n (%)	22 (44.0%)	9 (18.0%)	0.005
Prestroke antiplatelet use, n (%)	18 (36.0%)	14 (28.0%)	0.391
Regular antihypertensive therapy, n (%)	37 (74.0%)	29 (58.0%)	0.091
Total cholesterol, mmol/L	6.03 [5.62; 6.35]	5.65 [5.19; 6.02]	0.002
LDL cholesterol, mmol/L	4.29 [3.86; 4.67]	3.78 [3.26; 4.20]	<0.001
HDL cholesterol, mmol/L	0.95 [0.86; 1.02]	1.06 [1.02; 1.15]	<0.001
Triglycerides, mmol/L	1.58 [1.35; 1.94]	1.64 [1.35; 2.04]	0.664

Table 2. Computed tomography and computed tomographic angiography findings in patients with stenotic and non-stenotic extracranial atherosclerosis

Indicator	Stenotic atherosclerosis (n=50)	Non-stenotic atherosclerosis (n=50)	p
Brain CT performed	50 (100.0%)	50 (100.0%)	–
Computed tomographic angiography performed	39 (78.0%)	33 (66.0%)	0.181
ASPECTS, median [Q1; Q3]	8.0 [7.0; 8.8]	9.0 [8.0; 9.0]	<0.001
Early ischemic changes on CT	32 (64.0%)	31 (62.0%)	0.836
Hyperdense artery sign	13 (26.0%)	6 (12.0%)	0.074
Intracranial hemorrhage excluded	50 (100.0%)	50 (100.0%)	–
CTA stenosis by NASCET, %, median [Q1; Q3]	84.8 [77.1; 89.8]	35.2 [30.2; 40.2]	<0.001
No large-vessel occlusion on CTA	37 (94.9%)	33 (100.0%)	0.549
Good collateral status on CTA	30 (76.9%)	32 (97.0%)	0.035
Low-attenuation plaque on CTA	27 (69.2%)	30 (90.9%)	0.024
Rim sign on CTA	13 (33.3%)	11 (33.3%)	1.000
Intraluminal thrombus on CTA	13 (33.3%)	7 (21.2%)	0.253
Plaque ulceration on CTA	17 (43.6%)	11 (33.3%)	0.374

Notes: CTA – specific percentages were calculated among patients who underwent computed tomographic angiography: stenotic group, n=39; non-stenotic group, n=33;
ASPECTS – Alberta Stroke Program Early CT Score;
CTA – computed tomographic angiography;
CT – computed tomography;
NASCET – North American Symptomatic Carotid Endarterectomy Trial.

differences in good collateral status (p=0.035) and low-attenuation plaque (p=0.024) should be interpreted as hypothesis-generating rather than confirmatory.

Magnetic resonance imaging characteristics

Magnetic resonance imaging verified acute ischemic injury in all patients who underwent MRI. DWI positivity, ADC restriction and FLAIR positivity were present in 100% of MRI-examined patients in both groups. DWI/FLAIR mismatch was uncommon, indicating that only a small proportion of participants had a very early MRI time profile at examination.

Within the stenotic group, patients who underwent MRI (n=29) and those without MRI (n=21) did not differ materially by age, sex, NIHSS at admission, ASPECTS, culprit stenosis or plaque GSM: age 67.0 [64.0; 70.0] vs 65.0 [62.0; 68.0] years, p=0.296; NIHSS 10.0 [8.0; 14.0] vs 11.0 [7.0; 12.0], p=0.650; ASPECTS 8.0 [7.0; 9.0] vs 8.0 [7.0; 8.0], p=0.746; culprit stenosis 82.4 [74.9; 87.5]% vs 84.8 [76.3; 93.4]%, p=0.205; plaque GSM 62.0 [55.0; 68.0] vs 60.0 [58.0; 67.0], p=0.937. However, because MRI was not uniformly available, MRI-specific findings should be interpreted cautiously.

The two groups did not differ significantly in microbleed burden, Fazekas score or markers of chronic atrophic change. The main MRI differences concerned the acute ischemic lesion. Stenotic atherosclerosis was associated with a larger infarct volume. Infarct pattern differed significantly: watershed infarcts predominated in stenotic disease, whereas embolic-multifocal and

cortical patterns were more frequent in non-stenotic disease. This supports the coexistence of a hemodynamic mechanism in stenotic disease and an artery-to-artery embolic mechanism in vulnerable non-stenotic plaques (*Table 3*).

Ultrasonography, Doppler-derived hemodynamics and plaque morphology

Duplex ultrasonography clearly separated the groups by the degree of culprit artery stenosis.

Stenotic atherosclerosis was characterized by markedly higher PSV, EDV and ICA/CCA PSV ratio, confirming hemodynamic significance. Intima-media thickness was also greater in the stenotic group, which indicates a higher systemic atherosclerotic burden.

The plaque morphology profile differed in the opposite direction. Plaques were thicker and longer in stenotic disease, but the non-stenotic group had lower GSM, much higher frequency of GSM below 50, higher vulnerability score and a higher prevalence of thin or ruptured fibrous-cap signs. Calcified plaques were more frequent in the ste-

Table 3. Magnetic resonance imaging and infarct pattern in the study groups

Indicator	Stenotic atherosclerosis (n=50)	Non-stenotic atherosclerosis (n=50)	p
Brain MRI performed	29 (58.0%)	50 (100.0%)	<0.001
DWI-positive acute ischemic lesion	29 (100.0%)	50 (100.0%)	–
Restriction on ADC map	29 (100.0%)	50 (100.0%)	–
FLAIR-positive ischemic lesion	29 (100.0%)	50 (100.0%)	–
DWI/FLAIR mismatch	3 (10.3%)	2 (4.0%)	0.351
SWI microbleeds, median [Q1; Q3]	2.0 [1.0; 3.0]	2.0 [1.0; 3.0]	0.851
Fazekas score, median [Q1; Q3]	2.0 [1.0; 2.0]	2.0 [2.0; 2.0]	0.387
Ischemic lesion volume, ml, median [Q1; Q3]	47.9 [35.8; 55.8]	33.2 [23.6; 39.2]	<0.001
Middle cerebral artery territory	41 (82.0%)	38 (76.0%)	0.386
Cerebellar or vertebrobasilar territory	4 (8.0%)	9 (18.0%)	0.386
Cortical infarct pattern	10 (20.0%)	15 (30.0%)	0.033†
Embolic-multifocal infarct pattern	13 (26.0%)	22 (44.0%)	0.033†
Large subcortical infarct pattern	9 (18.0%)	6 (12.0%)	0.033†
Watershed infarct pattern	18 (36.0%)	7 (14.0%)	0.033†
Hemorrhagic transformation	13 (26.0%)	6 (12.0%)	0.074

Notes:

†p=0.033 refers to the global Pearson chi-square test for the four-category infarct pattern distribution. Individual row-wise p-values were not calculated and should not be inferred from this global test. In MRI-only sensitivity analysis, the pattern distribution difference was attenuated and did not reach statistical significance (p=0.121), so this result should be interpreted as exploratory;

ADC – apparent diffusion coefficient;

DWI – diffusion-weighted imaging;

FLAIR – fluid-attenuated inversion recovery;

MRI – magnetic resonance imaging;

SWI – susceptibility-weighted imaging.

DWI-, ADC-, FLAIR-, SWI- and Fazekas-related percentages were calculated among patients who underwent MRI: stenotic group, n=29; non-stenotic group, n=50

notic group, suggesting a more fibrotic-calcified obstructive phenotype. Non-stenotic disease therefore represented a smaller but more vulnerable plaque phenotype (*Table 4*).

The plaque vulnerability score summarizes ultrasound and vessel-wall imaging signs of instability. Group assignment was not based on the median right or left ICA stenosis separately. It was

Table 4. Duplex ultrasonography and plaque morphology in the study groups

Indicator	Stenotic atherosclerosis (n=50)	Non-stenotic atherosclerosis (n=50)	p
Culprit artery stenosis, %, median [Q1; Q3]	83.7 [75.7; 89.3]	35.7 [30.3; 39.4]	<0.001
Stenosis category below 50%	0 (0.0%)	50 (100.0%)	<0.001
Stenosis category [70÷99]%	47 (94.0%)	0 (0.0%)	<0.001
Occlusion or 100% stenosis	3 (6.0%)	0 (0.0%)	<0.001
Right internal carotid artery stenosis, %, median [Q1; Q3]	43.2 [28.6; 79.7]	27.4 [18.8; 34.9]	<0.001
Left internal carotid artery stenosis, %, median [Q1; Q3]	73.6 [33.9; 84.8]	29.1 [18.3; 37.3]	<0.001
Right common carotid intima-media thickness, mm, median [Q1; Q3]	1.18 [1.14; 1.24]	1.06 [0.99; 1.17]	<0.001
Left common carotid intima-media thickness, mm, median [Q1; Q3]	1.18 [1.12; 1.26]	1.05 [0.98; 1.16]	<0.001
Ipsilateral internal carotid artery PSV, m/s, median [Q1; Q3]	3.09 [2.80; 3.67]	1.27 [1.11; 1.42]	<0.001
Ipsilateral internal carotid artery EDV, m/s, median [Q1; Q3]	1.31 [1.06; 1.52]	0.53 [0.43; 0.64]	<0.001
Internal/common carotid artery PSV ratio, median [Q1; Q3]	3.08 [2.53; 3.83]	1.38 [1.18; 1.65]	<0.001
Plaque thickness, mm, median [Q1; Q3]	5.10 [4.43; 5.80]	3.85 [3.50; 4.38]	<0.001
Plaque length, mm, median [Q1; Q3]	17.0 [14.8; 19.4]	13.7 [12.6; 15.7]	<0.001
Echolucent plaque	29 (58.0%)	33 (66.0%)	0.410
Calcified plaque	29 (58.0%)	11 (22.0%)	<0.001
Plaque GSM, median [Q1; Q3]	61.5 [57.0; 67.8]	47.0 [38.2; 51.0]	<0.001
Plaque GSM below 50	5 (10.0%)	34 (68.0%)	<0.001
Lipid-rich necrotic core	23 (46.0%)	32 (64.0%)	0.070
Thin or ruptured fibrous cap	9 (18.0%)	21 (42.0%)	0.009
Plaque vulnerability score, median [Q1; Q3]	3.0 [2.0; 3.0]	4.0 [3.0; 5.0]	<0.001
High plaque vulnerability, four or more features	10 (20.0%)	32 (64.0%)	<0.001

Notes: EDV – end-diastolic velocity; GSM – gray-scale median; PSV – peak systolic velocity.

based on the culprit ipsilateral extracranial artery with the highest clinically relevant stenosis. In the stenotic group, all patients had at least one culprit extracranial artery with ≥50% stenosis; in this cohort, the culprit stenosis was ≥70% or occlusion in all stenotic cases. Side-specific right and left ICA stenosis values are descriptive and include non-culprit contralateral arteries; therefore, the median right ICA stenosis of 43.2% does not contradict stenotic-group allocation.

Integrated clinical-instrumental analysis

The integrated analysis combined neurological severity, functional status, neuroimaging burden, stenosis severity, Doppler hemodynamics and plaque vulnerability. Stenotic atherosclerosis was associated with a more severe clinical course, worse discharge functional status, lower ASPECTS and larger ischemic lesion volume. This profile corresponds to a large anatomical and hemodynamic injury phenotype.

Non-stenotic atherosclerosis had a different profile. Despite less luminal narrowing and lower flow velocities, it showed a lower GSM, higher vulnerability score, higher prevalence of high plaque vulnerability and more frequent early neurological deterioration. The latter result is clinically important because it suggests that non-stenotic plaques may be unstable and dynamically emboligenic rather than benign (*Table 5*).

Spearman correlation analysis showed that neurological deficit at admission was inversely associated with ASPECTS and directly associated with ischemic lesion volume, culprit artery stenosis and ipsilateral ICA PSV. Functional outcomes at discharge were most consistently associated with lesion volume. In contrast, the plaque vulnerability score did not correlate directly with baseline NIHSS, which supports the interpretation that vulnerability is more closely linked to embolic instability and early worsening than to baseline deficit severity alone (*Table 6*).

Table 5. Integrated clinical and instrumental profile of patients with stenotic and non-stenotic extracranial atherosclerosis

Indicator	Stenotic atherosclerosis (n=50)	Non-stenotic atherosclerosis (n=50)	p
NIHSS at admission, points, median [Q1; Q3]	10.0 [7.2; 13.0]	8.0 [6.2; 10.0]	0.011
Modified Rankin Scale at discharge, points, median [Q1; Q3]	3.0 [2.0; 4.0]	2.0 [2.0; 3.0]	0.013
Barthel Index at discharge, points, median [Q1; Q3]	38.0 [22.0; 58.2]	48.5 [39.2; 60.0]	0.023
ASPECTS, median [Q1; Q3]	8.0 [7.0; 8.8]	9.0 [8.0; 9.0]	<0.001
Ischemic lesion volume, ml, median [Q1; Q3]	47.9 [35.8; 55.8]	33.2 [23.6; 39.2]	<0.001
Culprit artery stenosis, %, median [Q1; Q3]	83.7 [75.7; 89.3]	35.7 [30.3; 39.4]	<0.001
Ipsilateral internal carotid artery PSV, m/s, median [Q1; Q3]	3.09 [2.80; 3.67]	1.27 [1.11; 1.42]	<0.001
Plaque GSM, median [Q1; Q3]	61.5 [57.0; 67.8]	47.0 [38.2; 51.0]	<0.001
Plaque vulnerability score, median [Q1; Q3]	3.0 [2.0; 3.0]	4.0 [3.0; 5.0]	<0.001
High plaque vulnerability	10 (20.0%)	32 (64.0%)	<0.001
Early neurological deterioration	4 (8.0%)	15 (30.0%)	0.005
Hemorrhagic transformation	13 (26.0%)	6 (12.0%)	0.074

Notes: NIHSS – National Institutes of Health Stroke Scale;
ASPECTS – Alberta Stroke Program Early CT Score;
GSM – gray-scale median; PSV – peak systolic velocity.

Table 6. Correlations between clinical and instrumental indicators

Pair of indicators	Spearman rho	p	n
NIHSS at admission – ASPECTS	–0.640	<0.001	100
NIHSS at admission – ischemic lesion volume	0.529	<0.001	100
NIHSS at admission – culprit artery stenosis	0.232	0.020	100
NIHSS at admission – ipsilateral internal carotid artery PSV	0.302	0.002	100
NIHSS at admission – plaque GSM	0.215	0.032	100
NIHSS at admission – plaque vulnerability score	–0.120	0.233	100
Barthel Index at discharge – ischemic lesion volume	–0.507	<0.001	100
Modified Rankin Scale at discharge – ischemic lesion volume	0.464	<0.001	100

Notes: ASPECTS – Alberta Stroke Program Early CT Score;
GSM – gray-scale median; NIHSS – National Institutes of Health Stroke Scale;
PSV – peak systolic velocity.

The weak direct unadjusted correlation between plaque GSM and NIHSS at admission (ρ=0.215, p=0.032) was unexpected and should not be interpreted as evidence that more echogenic plaque directly increases stroke severity. In this cohort, higher GSM was closely related to the stenotic/calcified obstructive phenotype and larger lesion burden; therefore, the association is likely confounded by stenosis severity and infarct volume. In an exploratory partial-rank analysis adjusted for ischemic lesion volume, culprit stenosis and age, the GSM–NIHSS association was no longer retained (partial $\rho \approx -0.10$, p=0.330). This finding was therefore interpreted cautiously as an unadjusted association rather than as an independent pathophysiological effect.

Discussion

The study demonstrates that stenotic and non-stenotic extracranial atherosclerosis in ischemic stroke represent different instrumental phenotypes. The stenotic phenotype was characterized by severe luminal narrowing, high Doppler velocities, lower ASPECTS, larger infarct volume and worse clinical-functional indices. These findings are consistent with a hemodynamic-stenotic mechanism, in which the magnitude of obstruction and flow acceleration contribute to larger ischemic injury and more severe neurological deficit.

The non-stenotic phenotype was clinically relevant for a different reason. Although luminal narrowing was below the conventional threshold of hemodynamic significance, the group had lower plaque GSM, higher vulnerability score, a higher frequency of high vulnerability, and more frequent early neurological deterioration. This aligns with the modern concept that non-stenotic plaques can be causative or contributory in ischemic stroke when they possess high-risk features. Systematic reviews have shown that recurrent stroke or transient ischemic attack risk in non-stenotic plaques is not negligible and increases in the presence of high-risk plaque characteristics [5]. Focused reviews also emphasize that plaque thickness, hypodensity, ulceration and intraplaque hemorrhage may identify a subgroup of patients in whom the plaque is not merely incidental [6].

Computed tomographic angiography findings in this study are important because low-attenuation plaque was more common in non-stenotic disease. CTA-based vessel wall assessment can detect hypodense plaque, calcification, ulceration and remodeling, thus extending acute stroke imaging beyond lumen-only interpretation [7; 8]. In our cohort, good collaterals were more frequent in the non-stenotic group, which may explain the smaller median infarct volume despite a higher plaque vulnerability burden.

The MRI pattern further supports mechanistic differentiation. Watershed infarcts were more frequent in stenotic disease, which is compatible with hypoperfusion or impaired reserve. Embolic-multifocal and cortical patterns were more frequent in

non-stenotic disease, which is compatible with artery-to-artery embolization from a vulnerable plaque. This observation is clinically actionable: a patient with non-stenotic stenosis by diameter criteria may still require intensified prevention, repeated vascular imaging and monitoring of plaque activity when MRI shows an embolic pattern and ultrasound or CTA show vulnerable morphology.

Ultrasound remains a practical first-line tool. The lower GSM and higher rate of GSM below 50 in the non-stenotic group indicate a lipid-rich or hemorrhagic plaque composition. Prior studies of carotid plaque echolucency and high-risk plaque features support the use of plaque morphology as a risk modifier rather than as a secondary descriptive characteristic only [10–12]. The present data therefore support a two-axis interpretation of extracranial atherosclerosis: the stenosis axis reflects hemodynamic obstruction, and the vulnerability axis reflects biological instability.

Taken together, the present findings support a transition from a stenosis-only model of extracranial atherosclerosis to an integrated stenosis and vulnerability model. In the stenotic group, the dominant clinical signal was related to luminal obstruction and hemodynamic burden: higher culprit-artery stenosis, higher ipsilateral internal carotid artery peak systolic velocity, lower ASPECTS, larger ischemic lesion volume and worse functional status at discharge. In contrast, the non-stenotic group showed a different risk profile: lower plaque GSM, higher plaque vulnerability score, more frequent high plaque vulnerability and more frequent early neurological deterioration. Therefore, non-stenotic extracranial atherosclerosis should not be interpreted as a benign condition solely because the percentage of luminal narrowing remains below the conventional threshold for hemodynamic significance.

This interpretation is consistent with recent evidence on symptomatic non-stenotic carotid disease. In the ESCAPE-NA1 analysis, Marko M. et al. (2024) [13] showed that non-stenotic carotid disease was present in 26.8% of patients classified as embolic stroke of undetermined source and was associated with ipsilateral ischemic stroke, supporting the role of non-stenotic carotid disease as a potential stroke etiology rather than an incidental imaging finding. The topical review by Savastano L. et al. (2024) [14] further emphasizes that a subset of embolic strokes may originate from disrupted non-stenotic plaques with high-risk features, particularly intraplaque hemorrhage, lipid-rich necrotic core, thinning or rupture of the fibrous cap and ulceration. The present study extends this concept to a comparative clinical-instrumental cohort by showing that non-stenotic plaques may have a more vulnerable morphology despite lower flow velocities and smaller luminal narrowing.

The imaging implications of these findings are also important. Jayanandaiah A. et al. (2024) [15] demonstrated that multiparametric carotid plaque MRI correlates well with histopathology in symptomatic carotid stenosis and can identify high-risk plaque characteristics such as intraplaque hemorrhage, lipid-rich necrotic core and ulceration with high diagnostic accuracy. This supports the use of dedicated plaque imaging as a complementary approach to routine lumen-based assessment. At the same time, the Plaque-RADS proposal by Saba L. et al. (2024) [16] provides a standardized framework for reporting carotid plaque composition and morphology across ultrasound, CTA and MRI, explicitly adding morphological risk assessment to the conventional stenosis parameter. In future studies, applying such a structured reporting system may improve reproducibility and allow the present ultrasound- and CTA-derived vulnerability features to be harmonized with an internationally comparable plaque-risk lexicon.

The biological interpretation of plaque vulnerability is supported by molecular data. Miceli G. et al. (2024) [17] describe vulnerable carotid plaques as heterogeneous inflammatory and thromboinflammatory lesions characterized by lipid-rich necrotic core, intraplaque hemorrhage, thin fibrous cap, ulceration, neovascularization, extracellular matrix degradation and activation of proteolytic pathways. In this context, lower GSM and higher vulnerability score in the non-stenotic group may be interpreted as imaging correlates of biological plaque instability rather than merely descriptive ultrasound findings. Matrix metalloproteinase-9 is especially relevant because it participates in extracellular matrix degradation and plaque destabilization and also has post-stroke effects on blood-brain barrier integrity. Guo P. et al. (2025) [18] emphasize that MMP-9 increases dynamically in the acute phase of ischemic stroke, may peak within the first 24 hours, and contributes to blood-brain barrier disruption, edema, neuroinflammation and hemorrhagic transformation. Thus, integration of MMP-9 and other atherogenesis markers with plaque imaging may improve future risk stratification in both stenotic and non-stenotic extracranial atherosclerosis.

These observations should be interpreted cautiously because CTA and MRI were not available

for all patients, and modality-specific comparisons remain partly exploratory. Nevertheless, the combined clinical, ultrasound, CTA and MRI pattern supports the practical conclusion that secondary prevention after ischemic stroke should not rely exclusively on percentage stenosis. A clinically meaningful approach should include two complementary axes: the hemodynamic axis, reflected by degree of stenosis and Doppler velocities, and the vulnerability axis, reflected by GSM, plaque morphology, CTA/MRI high-risk features and, in future models, circulating biomarkers such as P-selectin and MMP-9. Prospective follow-up with repeated plaque imaging and biomarker assessment is required to determine which non-stenotic plaques progress, which remain stable, and which are associated with recurrent ischemic events.

The study has several ***limitations***. First, the sample size was moderate. Second, CTA and MRI were not performed in all patients; therefore, modality-specific CTA and MRI findings, especially infarct pattern analyses, should be interpreted as exploratory. Third, MRI availability was unequal between groups; although the MRI and non-MRI subgroups within the stenotic group were similar in several key baseline variables, residual selection bias cannot be excluded. Fourth, formal blinded central imaging adjudication was not performed. Fifth, the observational design does not prove causality. All numerical results were verified against the final analytical database before resubmission.

Conclusions

1. Multimodal instrumental assessment make it possible to differentiate a hemodynamic-stenotic phenotype from a plaque-vulnerability phenotype in patients with ischemic stroke and extracranial atherosclerosis.

2. Stenotic atherosclerosis is associated with greater luminal narrowing, higher ipsilateral internal carotid artery flow velocities, lower ASPECTS, larger ischemic lesion volume and worse functional status at discharge. This supports the interpretation of stenotic disease as a phenotype of larger anatomical and hemodynamic injury.

3. Non-stenotic atherosclerosis is not instrumentally benign. It is associated with lower plaque gray-scale median, a higher plaque vulnerability score, more frequent high vulnerability and a higher frequency of early neurological deterioration. These findings support plaque-oriented risk assessment even when stenosis is below 50%.

4. Infarct pattern analysis suggests a mechanistic difference between groups: watershed injury was more typical of stenotic disease, whereas embolic-multifocal and cortical patterns were more common in non-stenotic disease.

5. Preventive strategy in ischemic stroke with extracranial atherosclerosis should not rely exclusively on the percentage of stenosis. It should integrate computed tomographic angiography, magnetic resonance imaging, ultrasonography, Doppler hemodynamics and plaque morphology.

Prospects for Further Researches

Further studies should prospectively validate an integrated prognostic model combining plaque morphology, CTA and MRI vessel-wall markers, serial ultrasound assessment, lipid profile, inflammatory biomarkers, P-selectin and matrix metalloproteinase-9. A clinically useful next step is a 6- to 12-month follow-up study of non-stenotic plaques with high vulnerability to determine predictors of stenosis progression, recurrent ischemic events and response to intensive secondary prevention.

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Declarations

Conflict of interest is absent.

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The author verified, corrected and approved all scientific content and accepts responsibility for the final text. The final statistical values, conclusions and interpretation are based on the author-provided research data.

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