

Association between ischaemic stroke aetiology and leptomeningeal collateral status: a retrospective cohort study

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Summary

INTRODUCTION: There is limited understanding of the pathomechanistic relationship between leptomeningeal collateral formation and ischaemic stroke aetiology. We aimed to assess the association of leptomeningeal collateral status and ischaemic stroke aetiology, using the widely recognised “Trial of Org 10172 in Acute Stroke Treatment” (TOAST) classification categorising strokes into five distinct aetiologies.

METHODS: Retrospective study of consecutively admitted adult ischaemic stroke patients at a Swiss stroke centre. Leptomeningeal collateral status was assessed on admission with single-phase CT-angiographies using a validated 4-point score. Patients were categorised into large-artery atherosclerosis (LAA), cardioembolic (CE), small-vessel disease (SVD) and cryptogenic (CG) according to the TOAST classification. We performed ordinal and binary (poor [collaterals filling $\leq 50\%$ of the occluded territory] vs good [collaterals filling $> 50\%$ of the occluded territory] collateralisation) logistic regression to evaluate the impact of TOAST aetiology on collateral status.

RESULTS: Among 191 patients, LAA patients had better collateral status compared to non-LAA aetiology (LAA: 2 vs CE: 2 vs SVD: 3 vs CG: 2, $P_{LAA \text{ vs non-LAA}} = 0.04$). In weighted multivariate logistic regression, LAA and SVD independently predicted better collateral status (binary models [adjusted odds ratio; aOR]: LAA: 3.72 [1.21–11.44] and SVD: 4.19 [1.21–14.52]; ordinal models [adjusted common odds ratio; acOR]: LAA: 2.26 [95% CI: 1.23–4.15] and SVD: 1.94 [1.03–3.66]), while CE predicted worse collateral status (binary models [aOR]: CE: 0.17 [0.07–0.41]; ordinal models [acOR]: CE: 0.24 [0.11–0.51]).

CONCLUSION: The aetiology of ischaemic stroke is associated with leptomeningeal collateral status on single-phase CT-angiography, with LAA and SVD predicting better and CE predicting worse collateral status.

Introduction

Leptomeningeal collaterals are important for understanding the temporal evolution of ischaemic injury associated with acute stroke and the efficacy of recanalisation therapies. Leptomeningeal collaterals provide alternative blood flow pathways in the event of disrupted anterograde arterial flow [1].

Good collateralisation is associated with favourable functional outcomes in patients with acute large-vessel occlusions [2–5]. Possible protective mechanisms include a longer tolerance to ischaemia and a better endovascular device efficacy in terms of successful thrombus removal and avoidance of distal embolisation [1–6].

Several studies have investigated factors influencing the leptomeningeal collateral status assessed on admission with CT-angiography, such as age, sex and the presence of cardiovascular risk factors [7–9]. Emerging evidence indicates that collateral status differs based on the ischaemic stroke aetiology [10]. Chronic hypoperfusion was shown to be associated with better collateral recruitment whereas cardioembolic stroke aetiology was associated with worse collateralisation, potentially contributing to poorer functional outcomes in these patients [10–12].

However, these previous studies focused on the comparison between large-artery atherosclerosis and cardioembolic stroke aetiology. To our knowledge, less attention has been paid to leptomeningeal collateral status in relation to a wider set of aetiologies.

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The primary aim of this retrospective study was to explore the association between ischaemic stroke aetiology, categorised according to the “Trial of Org 10172 in Acute Stroke Treatment” (TOAST) classification [13], and leptomeningeal collateral status, assessed by single-phase CT-angiography, in a Swiss cohort.

Materials and methods

Population and study design

For this single-centre cohort study, we screened 200 consecutive adult patients with acute ischaemic stroke included in the PLEURA study [14]. PLEURA included all consecutive patients aged at least 18 years who were treated for an ischaemic or haemorrhagic cerebrovascular event at the University Hospital Basel between January 2014 and May 2021 and underwent CT-angiography during the index hospitalisation. We excluded patients if CT-angiography was not performed or unavailable. For this study, stratification by stroke aetiology was based on the TOAST classification with the aim of including 50 consecutive patients for every TOAST subgroup. Patients with cryptogenic aetiology were used as a proof-of-concept category due to the exclusion of tangible stroke aetiologies inherent to this category. In this stratum, we did not expect any influence on the degree of collateralisation given the lack of a pathophysiological stroke correlate. Individuals with a stroke of “Other determined aetiology” were excluded from our analyses due to the inhomogeneous pathomechanistic composition of this group. We assessed demographics (age, sex), medical history (premorbid modified Rankin Scale [mRS] score), known or newly diagnosed vascular risk factors (arterial hypertension [$>140/90$ mm Hg], diabetes [without glucose intolerance], dyslipidaemia [lipid-lowering treatment or LDL cholesterol >2.6 mmol/l], smoking [actively smoking or stopped <2 years ago]), coronary artery disease, myocardial infarction, peripheral artery disease) and prior medication (antiplatelets, anticoagulants, antihypertensives, lipid-lowering drugs), admission characteristics (body mass index, systolic blood pressure, National Institutes of Health Stroke Scale [NIHSS] score, total cholesterol, LDL cholesterol, blood glucose) and acute treatment with recanalisation therapies (intravenous thrombolysis and endovascular treatment).

The study was reviewed and approved by the Ethics Committee Northwest and Central Switzerland (EKNZ; 2021-01185 and 2023-00268). The study protocol, anonymised data and statistical code can be provided upon reasonable request.

The need for informed consent was waived by the EKNZ (article 34 of the Human Research Act).

Classification of stroke aetiology according to TOAST criteria

We used the established TOAST criteria to classify the index stroke aetiology [13]. The TOAST classification distinguishes five aetiological subtypes: (1) large-artery atherosclerosis (LAA; $\geq 50\%$ stenosis), (2) cardioembolic (CE; excluding patent foramen ovale and other rare cardiac causes), (3) small-vessel disease (SVD), (4) stroke of other determined aetiology, and (5) cryptogenic (CG; defined as

unknown aetiology despite complete evaluation) [13]. Patients with more than one possible aetiology were excluded.

Assessment of leptomeningeal collateral status on single-phase CT-angiography

Collateral status was assessed visually using acquired baseline single-phase CT-angiography data with a previously validated 4-point scale [15] (0 points: no collaterals; 1 point: collaterals filling $\leq 50\%$ of the occluded territory; 2 points: collaterals filling $>50\%$ but $<100\%$ of the occluded territory; 3 points: collaterals filling 100% of the occluded territory). For this study, each CT-angiography set was consistently evaluated by two independent reviewers (LS and either AMT or CG) who were blinded to the clinical characteristics and functional outcomes. In cases without consensus between the first two reviewers, an additional rating was performed by a third assessor (TDD), with the majority consensus determining the collateral status rating.

Before assessing leptomeningeal collateral status for this study, all reviewers were required to score a standardised training dataset consisting of 30 CT-angiography images with axial maximum intensity projection reconstructions. To qualify as an assessor, a minimum agreement of 80% with the previously defined collateral status consensus had to be achieved, without any time limit for the scoring.

Statistical analysis

Dichotomous variables are expressed as counts (with percentages), continuous variables as medians (with interquartile ranges [IQR]). For descriptive analyses, we considered all included individuals. We used Pearson’s chi-square test, the Wilcoxon rank-sum test and two-tailed *t*-tests, as appropriate. Bonferroni correction was performed to account for multiple comparisons.

We performed univariate and multivariate binary (poor [collaterals filling $\leq 50\%$ of the occluded territory] vs good [collaterals filling $>50\%$ of the occluded territory] collateralisation; primary analysis) and ordinal (entire spectrum of collateral scores; secondary analysis) logistic regression to examine the effect of ischaemic stroke aetiology on collateral status. Univariate ordinal regression was used to identify covariables that were statistically significantly associated with the leptomeningeal collateral status. Subsequently, we fitted four separate multivariate ordinal regression models (one for each TOAST aetiology: LAA vs non-LAA, CE vs non-CE, SVD vs non-SVD, CG vs non-CG), adjusting for all covariables identified in univariate analyses and those previously described in the literature [7–9] as influencing leptomeningeal collateral recruitment. The included covariables were age, sex, arterial hypertension, dyslipidaemia and diabetes. We calculated adjusted predictions that reflect the probability of good collateralisation for each TOAST aetiology subgroup by holding the above-mentioned covariables at their average (for continuous variables) or reference category (for categorical variables). Only individuals with complete covariable sets were considered.

Weights (proportion of each TOAST aetiology of interest in the ischaemic stroke population divided by the respective proportions in the sample) were used for all analyses

to address potential over- or under-representation due to the study's sampling strategy. The proportion of each TOAST aetiology in the ischaemic stroke population was derived from data of the Swiss stroke registry (LAA 15%, CE 27%, SVD 11%, CG 31%) [16].

All analyses were performed with STATA version 17.0 (StataCorp LLC, College Station, Texas, USA). P values <0.05 were considered significant and 95% confidence intervals (CI) are reported.

Results

Baseline characteristics according to TOAST aetiology

We included 191 patients with acute ischaemic stroke (figure 1).

There were several observed differences between TOAST aetiology subgroups. The detailed comparisons are presented in table 1.

In summary, CE patients were the oldest (on average 9 years older than SVD patients; $p_{\text{overall}} = 0.002$), were more severely pre-morbidly functionally impaired ($p_{\text{overall}} < 0.001$), were most often pretreated with anticoagulants ($p_{\text{overall}} < 0.001$) and most affected by the index stroke (highest median NIHSS on admission, $p_{\text{overall}} < 0.001$). Regarding LAA aetiology, these patients had the highest proportion of smokers ($p_{\text{overall}} < 0.001$) and prior myocardial infarction ($p_{\text{overall}} = 0.01$). Hypertension was generally very prevalent in the cohort with an overall proportion of 81%, but was highest in the SVD group at 65%, where it was also the least pretreated with antihypertensive medication.

In line with these findings, SVD patients had the highest systolic blood pressure on admission ($p_{\text{overall}} < 0.001$) compared to the other TOAST subgroups.

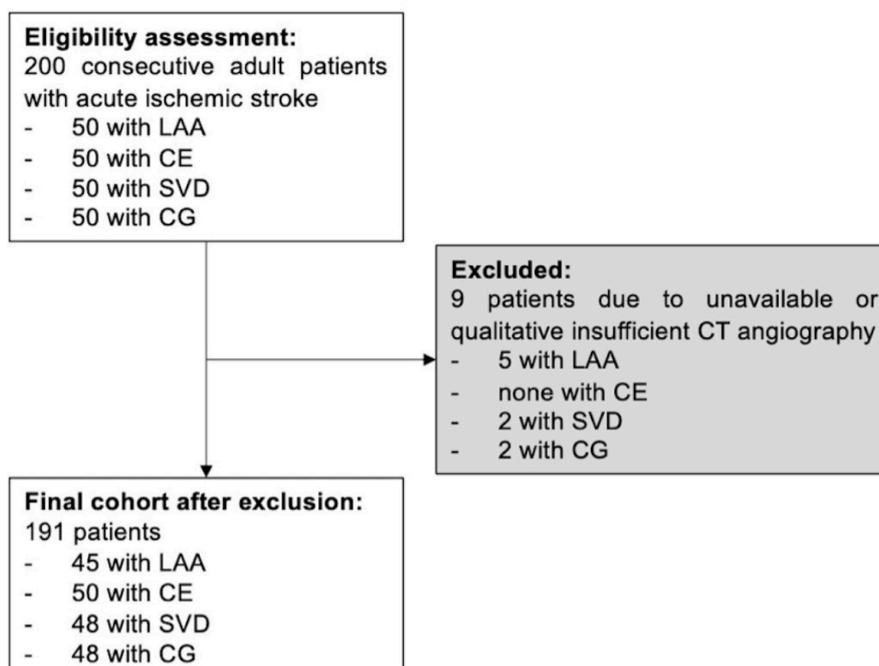
Collateral status and treatment characteristics stratified by TOAST aetiology

Concerning collateral scores, CE patients had the lowest collateral scores, whereas LAA and SVD patients had the highest ($p_{\text{overall}} < 0.001$) (table 1). Almost all SVD patients received intravenous thrombolysis (98%), followed by the clinically most severely affected CE group with 70% ($p_{\text{overall}} < 0.001$). The latter group was also the most likely to receive endovascular treatment (64%; $p_{\text{overall}} < 0.001$).

Impact of TOAST aetiology on collateral status

In the unadjusted analyses, LAA and SVD had the strongest association with good collateralisation (LAA: odds ratio [OR] 3.73, 95% confidence interval [CI] 1.24–11.23; SVD: OR 3.84, 95% CI 1.28–11.50) (table 2), CE with poor collateralisation (OR 0.15, 95% CI 0.07–0.33). After adjustment for significant covariables from the univariate analyses (table 3) as well as prespecified predictors of collateralisation, the associations were shown to be consistent in the binary and ordinal logistic models (table 2). For CG aetiology, there was no significant effect on the collateral status in either the unadjusted or adjusted models. Figure 2 illustrates the predicted probabilities of good collateralisation for different TOAST aetiologies.

Figure 1: Flowchart of the study. LAA: large-artery atherosclerosis; CE: cardioembolic; SVD: small-vessel disease; CG: cryptogenic.



Discussion

In a Swiss cohort of consecutive patients admitted for acute ischaemic stroke, we demonstrated that: (1) the TOAST subgroups differed considerably from one another with regard to several baseline characteristics, in particular traditional vascular risk factors; (2) collateral status varied across a wide range of TOAST aetiologies; and (3) LAA and SVD independently predicted favourable and CE unfavourable collateral status.

Our results are in line with those of a recent meta-analysis of seven studies that investigated the association of leptomeningeal collateral status with LAA and CE aetiology and found that LAA aetiology was associated with better collateralisation, and CE aetiology with worse collateralisation [17]. In contrast to the meta-analysis, we did not restrict to patients who received reperfusion therapies. It should also be noted that the type of collateral assessment varied among the studies included in the meta-analysis (i.e. multi-phase CT-angiography, cerebral angiography),

Table 1:
Baseline characteristics of acute ischaemic stroke patients according to TOAST aetiology.

		Total (n = 191)	Stroke aetiology according to TOAST				p value	Missing, n (%)
			LAA (n = 45)	CE (n = 50)	SVD (n = 48)	CG (n = 48)		
Demographics	Age in years, median (IQR)	78 (68–85)	76 (68–82)	82 (77–86)	73 (64–82)	77 (68–83)	0.002 ^a	0 (0%)
	Female, n (%)	72 (38%)	12 (27%)	21 (42%)	17 (35%)	22 (46%)	0.24	0 (0%)
Patient characteristics, n (%)	Premorbid modified Rankin Scale, median (IQR)	0 (0–1)	0 (0–0)	1 (0–2)	0 (0–1)	0 (0–1)	<0.001 ^b	21 (11%)
	Arterial hypertension, n (%)	154 (81%)	36 (80%)	44 (88%)	31 (65%)	43 (90%)	0.01 ^c	0 (0%)
	Diabetes, n (%)	41 (22%)	9 (20%)	10 (20%)	13 (27%)	9 (19%)	0.75	0 (0%)
	Dyslipidaemia, n (%)	112 (59%)	28 (62%)	27 (54%)	24 (50%)	33 (69%)	0.24	0 (0%)
	Smoking, n (%)	56 (29%)	28 (62%)	7 (14%)	11 (23%)	10 (21%)	<0.001 ^d	0 (0%)
	Coronary artery disease, n (%)	43 (23%)	12 (27%)	11 (22%)	8 (17%)	12 (28%)	0.57	5 (3%)
	Myocardial infarction, n (%)	20 (11%)	9 (20%)	8 (16%)	1 (2%)	2 (4%)	0.01 ^e	0 (0%)
	Peripheral artery disease, n (%)	7 (4%)	3 (7%)	2 (4%)	1 (2%)	1 (3%)	0.66	8 (4%)
Prior medication, n (%)	Antiplatelets	78 (41%)	22 (49%)	14 (28%)	19 (40%)	23 (48%)	0.13	0 (0%)
	Anticoagulants	23 (12%)	6 (13%)	14 (28%)	0 (0%)	3 (6%)	<0.001 ^f	1 (1%)
	Antihypertensives	126 (66%)	32 (71%)	38 (78%)	21 (44%)	35 (73%)	0.002 ^g	1 (1%)
	Lipid-lowering drugs	57 (30%)	18 (40%)	9 (18%)	13 (27%)	17 (35%)	0.10	1 (1%)
Admission characteristics	BMI in kg/m ² , median (IQR)	25 (23–28)	25 (23–27)	25 (23–28)	26 (23–28)	27 (24–29)	0.69	11 (6%)
	Systolic blood pressure in mm Hg, median (IQR)	153 (139–172)	141 (125–150)	155 (135–170)	163 (150–184)	153 (138–178)	<0.001 ^h	0 (0%)
	NIHSS on admission, median (IQR)	5 (2–9)	1 (0–4)	10 (6–16)	5 (3–8)	3 (0–7)	<0.001 ⁱ	2 (1%)
	Collateral score, median (IQR)	2 (2–3)	2 (2–3)	2 (1–2)	2 (2–3)	2 (2–3)	<0.001 ^j	0 (0%)
	Collateral score, mean (standard deviation)	2.1 (0.9)	2.4 (0.7)	1.6 (1.0)	2.4 (0.7)	2.2 (0.8)		
Laboratory parameters on admission, median (IQR)	Total cholesterol in mmol/l	4.7 (4.0–5.4)	4.4 (3.7–5.4)	4.5 (3.7–5.1)	4.8 (4.2–5.6)	4.9 (4.2–5.6)	0.09	5 (3%)
	LDL cholesterol in mmol/l	2.5 (2.0–3.2)	2.4 (1.8–3.4)	2.4 (1.9–2.9)	2.7 (2.1–3.2)	2.8 (2.2–3.3)	0.10	7 (4%)
	Glucose in mmol/l	6.4 (5.5–7.7)	5.6 (5.0–6.6)	7.1 (6.1–8.4)	6.2 (5.4–8.5)	6.5 (5.9–7.8)	<0.001 ^k	4 (2%)
Treatment characteristics, n (%)	Intravenous thrombolysis	101 (53%)	7 (16%)	35 (70%)	47 (98%)	12 (25%)	<0.001 ^l	0 (0%)
	Endovascular treatment	39 (20%)	6 (13%)	32 (64%)	1 (2%)	0 (0%)	<0.001 ^m	0 (0%)

CE: cardioembolic; CG: cryptogenic; eGFR: estimated glomerular filtration rate; INR: International Normalised Ratio; LAA: large-artery atherosclerosis; LDL: low-density lipoprotein; NIHSS: National Institutes of Health Stroke Scale; SVD: small-vessel disease; TOAST: Trial of Org 10172 in Acute Stroke Treatment

To identify which specific TOAST categories differ from each other, Bonferroni-corrected post-hoc tests were used (for continuous variables: ANOVA and Kruskal-Wallis test [for continuous variables with non-normal distribution]; for categorical variables: logistic regression with pairwise comparisons and Bonferroni adjustment). Statistically significant differences were found for:

a: CE vs SVD

b: LAA vs CE, CE vs CG

c: SVD vs CG

d: LAA vs CE, LAA vs SVD, LAA vs CG

e: Trend for differences for LAA vs SVD ($p = 0.02$), LAA vs CG ($p = 0.03$) and CE vs SVD ($p = 0.04$) which, however, did exceed the Bonferroni-corrected alpha level of ≈ 0.0083 .

f: No statistically significant results after application of Bonferroni correction; probably model-related estimation problem due to zero cell count in the SVD group (no patients with previous anticoagulants).

g: CE vs SVD, SVD vs CG

h: LAA vs CE, LAA vs SVD, LAA vs CG

i: LAA vs CE, LAA vs SVD, CE vs SVD, CE vs CG

j: LAA vs CE, CE vs SVD, CE vs CG

k: LAA vs CE, LAA vs SVD, LAA vs CG

l: LAA vs CE, LAA vs SVD, CE vs SVD, CE vs CG, SVD vs CG

m: LAA vs CE, CE vs SVD, CE vs CG

which may have led to different assessments of the degree of collateralisation.

Leptomeningeal collateralisation has been intensively studied in its practical application for radiological patient selection for endovascular therapies as well as prognostication of reperfusion injury thereafter. Currently, there are no established pharmacological or interventional approaches to modulate leptomeningeal collateral flow in acute ischaemic stroke. This may partly be due to limited knowledge of the underlying mechanisms of collateral formation.

The relationship between the degree of leptomeningeal collateralisation and functional outcome in patients with ischaemic stroke due to large-vessel occlusions has been described in detail previously [2, 18, 3, 19, 20]. In these stud-

ies, better collateral status was shown to be an independent predictor of a favourable long-term functional outcome. In the ESCAPE trial, which compared endovascular therapy within 12 hours after symptom onset with standard medical therapy, patients with poor collateralisation – used as a surrogate of a large ischaemic core – were excluded a priori [18]. In the time window up to 24 hours after stroke onset, the recent MR CLEAN-LATE trial demonstrated that patient selection based on collateral status for endovascular treatment is feasible, including patients with poor collateralisation (grades 0 and 1) [21].

However, a substantial proportion of patients with successful mechanical recanalisation do not show significant clinical improvement [22, 23]. To date, little is known about the underlying pathophysiological mechanisms. Recent trans-

Table 2:
Impact of stroke aetiology on collateralisation status.

			OR	95% CI	p value
Univariate logistic regression*	Binary (dichotomised collateral score) – good (vs bad) collateralisation**	LAA (vs non-LAA)	3.73	1.24–11.23	0.02
		CE (vs non-CE)	0.15	0.07–0.33	<0.001
		SVD (vs non-SVD)	3.84	1.28–11.50	0.02
		CG (vs non-CG)	2.37	0.96–5.85	0.06
	Ordinal (collateral score) – shift towards higher collateral score category	LAA (vs non-LAA)	2.15	1.19–3.91	0.01
		CE (vs non-CE)	0.22	0.11–0.45	<0.001
		SVD (vs non-SVD)	2.02	1.14–3.57	0.02
		CG (vs non-CG)	1.57	0.88–2.78	0.13
Multivariate logistic regression***	Binary (dichotomised collateral score) – good (vs bad) collateralisation**	LAA (vs non-LAA)	3.72	1.21–11.44	0.02
		CE (vs non-CE)	0.17	0.07–0.41	<0.001
		SVD (vs non-SVD)	4.19	1.21–14.52	0.02
		CG (vs non-CG)	1.99	0.76–5.20	0.16
	Ordinal (collateral score) – shift towards higher collateral score category	LAA (vs non-LAA)	2.26	1.23–4.15	0.01
		CE (vs non-CE)	0.24	0.11–0.51	<0.001
		SVD (vs non-SVD)	1.94	1.03–3.66	0.04
		CG (vs non-CG)	1.41	0.76–2.63	0.27

According to TOAST (Trial of Org 10 172 in Acute Stroke Treatment) classification: LAA: large-artery atherosclerosis; CE: cardioembolic; SVD: small-vessel disease; CG: cryptogenic. Collateral score: 0 = absent collaterals, 1 = collaterals filling ≤50% of the occluded territory, 2 = collaterals filling >50% but <100% of the occluded territory, 3 = collaterals filling 100% of the occluded territory.

* Unadjusted odds ratios (OR) (binary regression) and common odds ratios (cOR) (ordinal regression) are reported. We state 95% confidence intervals (CI).

** Good collateralisation: defined as collateral filling of >50% of the occluded territory.

*** Adjusted odds ratios (aOR) (binary regression) and adjusted common odds ratios (acOR) (ordinal regression) are reported. We state 95% confidence intervals (CI).

Table 3:
Univariate analysis of the association between baseline patient characteristics and shift towards higher collateral score.

	cOR	95% CI	p value
Age*	0.97	0.95–1.00	0.04
Female sex**	1.44	0.79–2.63	0.23
Premorbid mRS*	0.75	0.52–1.06	0.10
Arterial hypertension***	0.88	0.42–1.83	0.73
Diabetes***	1.02	0.52–1.97	0.96
Dyslipidaemia***	1.08	0.58–1.99	0.82
Smoking***	1.30	0.74–2.32	0.36
Coronary artery disease***	0.64	0.37–1.13	0.13
Myocardial infarction***	0.42	0.17–1.05	0.06
Peripheral artery disease***	0.58	0.26–1.30	0.19
Prior antiplatelets***	0.81	0.46–1.42	0.46
Prior anticoagulants***	0.93	0.31–2.81	0.89
Prior antihypertensives***	0.76	0.41–1.41	0.39
Prior lipid-lowering drugs***	0.97	0.52–1.78	0.91

cOR: common odds ratio; mRS: modified Rankin Scale.

* Interpretation of the coefficients: change in the log odds of a shift towards higher collateral score category for one unit increase in the predictor variable (e.g. age: per 1 year increase)

** Female vs male

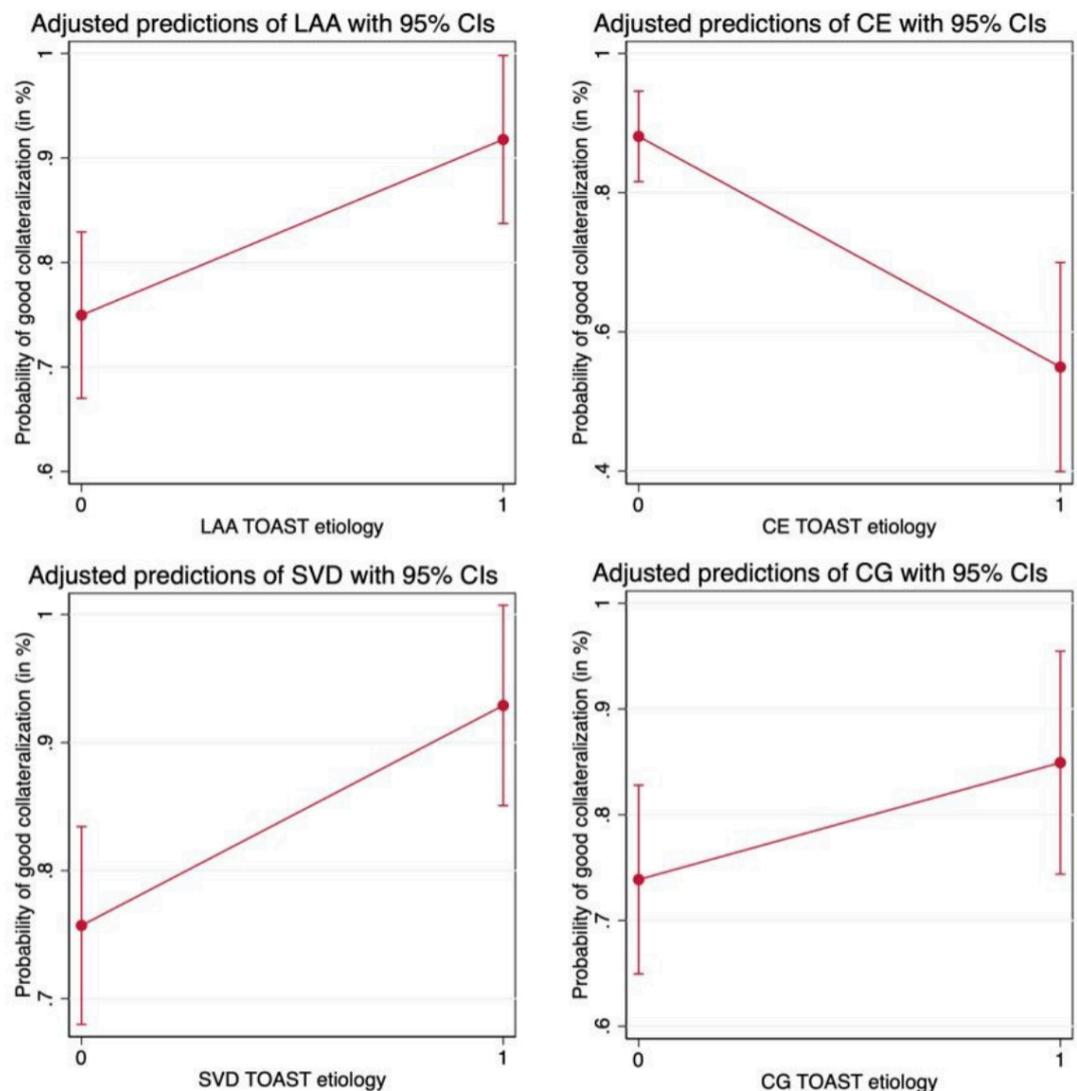
*** Present vs not present

lational work involving 33 stroke patients with M1 or M2 segment occlusion of the middle cerebral artery suggests a pivotal role of the leptomeningeal collateral status [24]. Poor collateralisation in patients who received rapid successful mechanical reperfusion was associated with haemorrhagic transformation and higher disability [24].

Clinical determinants of collateral formation may provide indirect pathophysiological insights regarding collateral formation. Since ischaemic stroke represents a heterogeneous pathophysiological group, it is reasonable to investigate to what extent different underlying aetiologies influence collateral formation. We are not yet aware of any investigation focusing on the association of leptomeningeal collateralisation with different stroke aetiologies across a broad TOAST range. We can only speculate about the reasons. Probably the most relevant is that the single-phase CT-angiography collateral scores (such as the one proposed by Tan et al. that we used) [15] have only been validated for middle cerebral artery occlusions with or without concomitant internal carotid artery occlusion. Thus, the consideration of SVD and cryptogenic embolic

strokes without the above-mentioned proximal vessel occlusion does not seem obvious. However, we believe that an exploratory study such as the one we conducted is justified. This is particularly due to its potential to generate pathophysiological hypotheses that need to be verified in future studies with larger case numbers. Chronic progressive hypoperfusion has been suggested as a possible driver of collateral formation, which could contribute to leptomeningeal collateralisation through activation of endothelial cells with consecutive activation of further downstream cascades [17]. This hypothesis would explain an association between the chronic impact of atherosclerotic plaques on haemodynamics in the context of LAA with better leptomeningeal collateral status via chronic stimulation of endothelial cells by shear forces [17]. In contrast, CE-induced ischaemia is not linked to chronic cerebral hypoperfusion that could promote collateral formation following this logic [17]. Data on leptomeningeal collateral status related to other TOAST subcategories are sparse. In our study, we saw that SVD aetiology independently predicted better leptomeningeal collateral status. It seems

Figure 2: Illustration of the predicted probabilities of good collateralisation (collaterals filling >50% of the occluded territory) for different TOAST aetiologies adjusted for covariables. Adjustment was performed for the following covariables: age, sex, arterial hypertension, dyslipidaemia and diabetes. LAA: large-artery atherosclerosis; CE: cardioembolic; SVD: small-vessel disease; CG: cryptogenic.



possible, considering the endothelial activation hypothesis, that progressive injury to the cerebral microperfusion with consecutive endothelial upregulation of several transcription factors and adhesion molecules might contribute to better collateral formation [25]. However, these results must be interpreted with caution given the limited number of cases and require further investigation in larger cohorts. In our study, we included patients without any detectable cardiac embolic source, relevant microangiopathy or macroangiopathy after aetiologic workup as a proof-of-concept subgroup. The fact that we did not see an association with leptomeningeal collateral status in this group reinforces a pathomechanistic link between stroke aetiology and collateral formation.

Strengths and limitations

Our study has several strengths and limitations.

Strengths are that: (1) we included consecutive patients from clinical practice; (2) we studied the full spectrum of stroke aetiologies also including patients with cryptogenic aetiology; (3) leptomeningeal collateral status was assessed by at least two independent assessors; (4) collateral assessment was consistently performed using single-phase CT-angiography.

Limitations include: (1) the small sample size per aetiological subgroup and the potential for TOAST misclassification; (2) missing information on occlusion localisation (which could have influenced the degree of collateralisation) for non-lacunar strokes. However, we did assess the NIHSS score, which can serve as a clinical surrogate marker for occlusion site; (3) well-known limitations of single-phase CT-angiography, whose correct interpretability depends on image acquisition during the arterial phase; (4) the limited generalisability of our findings due to the single-centre retrospective design. The applicability of our results to broader populations may therefore be limited given potential differences in, for example, patient demographics, healthcare systems and stroke management protocols.

Conclusion

The aetiology of ischaemic stroke is associated with leptomeningeal collateral status on baseline single-phase CT-angiography. Large-artery atherosclerosis and small-vessel disease are associated with better collateral status, while cardioembolic aetiology is linked to worse collateral status.

Data availability statement

Data may be provided upon reasonable request to the corresponding authors.

Acknowledgments

Author contributions: LS, AMT, TDD and GMDM planned the work. LS, AMT and CG collected the data. LS, AMT, TDD and GMDM drafted the manuscript. TDD performed the statistical analyses. All authors interpreted the results and contributed significantly to the final manuscript.

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Potential competing interests

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