Brain edema growth after thrombectomy is associated with comprehensive collateral blood flow

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ABSTRACT

Background We determined whether a comprehensive assessment of cerebral collateral blood flow is associated with ischemic lesion edema growth in patients successfully treated by thrombectomy.

Methods This was a multicenter retrospective study of ischemic stroke patients who underwent thrombectomy treatment of large vessel occlusions. Collateral status was determined using the cerebral collateral cascade (CCC) model, which comprises three components: arterial collaterals (Tan Scale) and venous outflow profiles (Cortical Vein Opacification Score) on CT angiography, and tissue-level collaterals (hypoperfusion intensity ratio) on CT perfusion. Quantitative ischemic lesion net water uptake (NWU) was used to determine edema growth between admission and follow-up non-contrast head CT (ΔNWU). Three groups were defined: CCC+ (good pial collaterals, tissue-level collaterals, and venous outflow), CCC− (poor pial collaterals, tissue-level collaterals, and venous outflow), and CCCmixed (remainder of patients). Primary outcome was ischemic lesion edema growth (ΔNWU). Multivariable regression models were used to assess the primary and secondary outcomes.

Results 538 patients were included. 157 patients had CCC+, 274 patients CCCmixed, and 107 patients CCC− profiles. Multivariable regression analysis showed that compared with patients with CCC+ profiles, CCC− (β 1.99, 95% CI 0.68 to 3.30, P=0.003) and CCCmixed (β 1.65, 95% CI 0.75 to 2.56, P<0.001) profiles were associated with greater ischemic lesion edema growth (ΔNWU) after successful thrombectomy treatment. ΔNWU (OR 0.74, 95% CI 0.68 to 0.8, P<0.001) and CCC+ (OR 13.39, 95% CI 4.88 to 36.76, P<0.001) were independently associated with functional independence.

Conclusion A comprehensive assessment of cerebral collaterals using the CCC model is strongly associated with edema growth and functional independence in acute stroke patients successfully treated by endovascular thrombectomy.

INTRODUCTION

Endovascular thrombectomy (EVT) has become the standard of care for the treatment of patients with acute ischemic stroke and large vessel occlusion (AIS-LVO).1 Timely restoration of blood flow to ischemic brain tissue is crucial for a potential neurologically recovery of these patients. However, poor clinical outcomes are still observed in a substantial number of patients treated by EVT despite successful vessel reperfusion.2 3 One explanation for that may be the occurrence of extensive brain edema formation, which is strongly related to collateral blood flow during the period of brain ischemia.4 5 Consequently, reliable imaging biomarkers that identify patients at risk of brain edema growth are needed.

Cerebral edema can be quantified directly by ischemic lesion net water uptake (NWU) using densitometry of hypoattenuated infarct areas.
on non-contrast head CT. Extensive ischemic lesion NWU correlates with poor microvascular perfusion status and more severe ischemic damage to the brain tissue. However, successful vessel reperfusion during EVT was found to be associated with reduced formation of ischemic brain edema. A favorable collateral status is associated with better procedural and clinical outcomes of AIS-LVO patients after thrombectomy treatment. Notably, quantitative changes of NWU over time also seem to be linked to the cerebral collateral status. A favorable collateral status is associated with brain edema growth in AIS-LVO patients successfully treated by thrombectomy. We hypothesized that favorable collateral profiles on all three levels of the collateral cascade and allows for a more comprehensive assessment of collateral blood flow to and through the ischemic brain tissue into subsequent cortical veins. However, it remains unclear whether the CCC model correlates with ischemic brain edema growth following thrombectomy in AIS-LVO patients.

In this study, we aimed to investigate whether distinct collateral blood flow patterns determined by the CCC model are associated with brain edema growth in AIS-LVO patients successfully treated by thrombectomy. We hypothesized that favorable collateral profiles on all three distinct levels of the collateral cascade are associated with reduced brain edema growth compared with patients with less favorable collateral profiles, and that both less edema growth and favorable collateral profiles are correlated with good clinical outcomes. Our findings may have important implications for cerebral edema biology and stroke pathophysiology in the setting of AIS-LVO.

METHODS
Study design
This was a retrospective multicenter cohort study of AIS-LVO patients treated by endovascular thrombectomy at two comprehensive stroke centers (University Medical Center Hamburg-Eppendorf, Germany, and Stanford University Hospital, USA) between May 2015 and December 2021.

Standard protocol approvals, registrations, and patient consents
The study protocol was approved by the institutional review boards of both study centers (ID 689–15), complied with the Health Insurance Portability and Accountability Act (HIPAA), and followed the guidelines of the Declaration of Helsinki. Patient informed consent was waived by our review boards for this retrospective study. This study reports against the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for medical research.

Patient inclusion, population, and clinical data
Patient data were obtained from prospectively maintained stroke databases at each center. Inclusion criteria were: (1) patients with AIS-LVO treated by thrombectomy; (2) multimodal imaging assessment on patient admission including non-contrast head CT, CT angiography with homogeneous opacification of the superior sagittal, transverse, and sigmoid dural venous sinuses to allow for CT angiography collateral status, and venous outflow determination and interpretable CT perfusion imaging studies; (3) anterior circulation large vessel occlusion of the internal carotid artery or first (M1) or second (M2) segment of the middle cerebral artery; (4) successful vessel recanalization during EVT (defined as modified Thrombolysis In Cerebral Infarction Score (TICI) 2b-3); (5) availability of a non-contrast head CT 24–48 hours following EVT to determine post-treatment NWU.

Exclusion criteria were: (1) poor CT angiography image quality due to excessive patient motion or incomplete contrast opacification of target cerebral arteries and veins; (2) poor CT perfusion image quality due to excessive motion degradation or failed contrast bolus.

Imaging analysis
All perfusion imaging studies were automatically analyzed with RAPID (SchemaView, Menlo Park, CA).

The three components of the CCC model were analyzed according to the approach described by Faizy et al. Pial arterial collaterals were assessed using the Tan scale on CT angiography images by consensus reading of two neuroradiologists (TDF and JH with 11 and 16 years of experience, respectively). Good collaterals were defined as filling of ≥50%, and poor collaterals were defined as <50% filling of the middle cerebral artery territory.

The hypoperfusion intensity ratio (HIR), defined as volume of brain tissue with a delay of Tmax > 10 s divided by the volume of brain tissue with a Tmax delay of ≥6 s, was automatically derived from CT perfusion imaging to determine tissue-level collaterals. Favorable tissue-level collaterals were defined as HIR ≤0.4, whereas poor tissue-level collaterals were defined as HIR >0.4.

Venous outflow profiles were determined by two experienced neuroradiologists (TDF, JH) in the vein of Labbé, sphenoparietal sinus, and superficial middle cerebral vein using the Cortical Vein Opacification Score (COVES) on single-phase CT angiography. Discrepancies were settled by consensus. Favorable venous outflow was defined as a score of 3–6 and unfavorable venous outflow was regarded a score of 0–2.

Successful vessel recanalization after thrombectomy treatment was defined as modified TICI scores of 2b-3.

The Alberta Stroke Program Early CT Score (ASPECTS) was determined on pre-treatment head non-contrast CT images.

Ischemic lesion NWU (%) was determined on both admission and follow-up non-contrast head CT images as described by Broocks et al. The density of ischemic tissue was measured in a region of interest (ROI) defining the demarcated hypoattenuated ischemic lesion on non-contrast head CTs. The corresponding normal density was defined as an ROI mirrored symmetrically to the non-ischemic hemisphere and adjusted anatomically to exclude sulci and cerebrospinal fluid. NWU was calculated per volume of infarct. Ischemic lesion edema growth (∆NWU) was specified as the difference of NWU at follow-up and on admission.

Study group definitions
A favorable (CCC+) profile was defined as: Tan ≥50%, HIR ≤0.4, and COVES of 3–6. An unfavorable (CCC−) profile was regarded as: Tan <50%, HIR >0.4, and COVES of 0–2. CCCmixed profiles were assigned to patients who did not fulfill the criteria of the CCC+ or CCC− groups.

Outcome measures
Primary outcome was ischemic lesion edema growth (∆NWU) between patient admission and follow-up after thrombectomy treatment. Secondary outcome was favorable functional outcome

defined as functional independence (mRS score of 0–2) 90 days after thrombectomy treatment.

**Statistical analysis**
Continuous and ordinal variables were described by median (IQR) and categorical variables by N (%). Patient demographics, clinical variables, and neuroimaging data were compared between either two or three CCC groups using χ² tests, and Mann Whitney U or Kruskal-Wallis tests, or trend statistics (Cochran-Armitage Trend Test or Jonckheere-Terpstra Test for Ordered Alternatives), respectively. Clinical and imaging variables association with ΔNWU and functional outcome was assessed using multivariable models: univariate general linear model, and binary logistic regression, respectively. The models were adjusted for imbalances between CCC groups: age, presentation National Institutes of Health Stroke Scale (NIHSS), serum glucose at enrollment, penumbra and estimated core volumes determined by CT perfusion, admission ASPECTS, and vessel occlusion localization. ΔNWU was added as an independent variable for functional outcome model. α was set at the 0.05 level, and all reported results are two-sided. Statistical analysis was done using IBM SPSS statistics, v. 28.0 and SAS 9.4.

**RESULTS**
A total number of 813 patients underwent thrombectomy triage, and 538 met inclusion criteria (online supplemental figure 1).

**Table 1** Patient characteristics and stroke presentation details

<table>
<thead>
<tr>
<th></th>
<th>CCC+ (n=157)</th>
<th>CCCmixed (n=274)</th>
<th>CCC− (n=107)</th>
<th>P value (difference between groups)</th>
<th>P value (trend test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>72 (61–80)</td>
<td>75 (64–83)</td>
<td>77 (68–83)</td>
<td>0.002</td>
<td>&lt;0.001</td>
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<tr>
<td>Female, n (%)</td>
<td>81 (52)</td>
<td>131 (48)</td>
<td>52 (49)</td>
<td>0.75</td>
<td>0.58</td>
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<tr>
<td>Medical history</td>
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<td>Atrial fibrillation, n (%)</td>
<td>65 (41)</td>
<td>110 (40)</td>
<td>53 (50)</td>
<td>0.24</td>
<td>0.25</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>105 (67)</td>
<td>187 (68)</td>
<td>75 (70)</td>
<td>0.86</td>
<td>0.58</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>50 (34)</td>
<td>72 (29)</td>
<td>20 (22)</td>
<td>0.12</td>
<td>0.04</td>
</tr>
<tr>
<td>Blood glucose (mg/dL), median (IQR)</td>
<td>116 (99–141)</td>
<td>122 (105–153)</td>
<td>121 (106–157)</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>30 (19)</td>
<td>56 (20)</td>
<td>22 (21)</td>
<td>0.94</td>
<td>0.75</td>
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<tr>
<td>Systolic blood pressure (mm Hg), median (IQR)</td>
<td>149 (132–163)</td>
<td>152 (133–170)</td>
<td>157 (132–180)</td>
<td>0.09</td>
<td>0.03</td>
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<tr>
<td>Smoking</td>
<td></td>
<td></td>
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<tr>
<td>Current smoker, n (%)</td>
<td>13 (8)</td>
<td>33 (12)</td>
<td>16 (15)</td>
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</tr>
<tr>
<td>Never smoked, n (%)</td>
<td>110 (70)</td>
<td>191 (70)</td>
<td>76 (71)</td>
<td></td>
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<tr>
<td>Prior smokers, n (%)</td>
<td>26 (17)</td>
<td>38 (14)</td>
<td>9 (8)</td>
<td></td>
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<tr>
<td>Unknown smoking status, n (%)</td>
<td>8 (5)</td>
<td>12 (4)</td>
<td>6 (6)</td>
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<tr>
<td>Stroke presentation details</td>
<td></td>
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<tr>
<td>Presentation NIHSS, median (IQR)</td>
<td>10 (6–14)</td>
<td>15 (10–19)</td>
<td>18 (15–21)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from symptom onset to alteplase administration (min), median (IQR)</td>
<td>109 (75–160)</td>
<td>90 (70–146)</td>
<td>110 (63–146)</td>
<td>0.43</td>
<td>0.28</td>
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<tr>
<td>Treatment details</td>
<td></td>
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<tr>
<td>Intravenous thrombolysis administration, n (%)</td>
<td>95 (61)</td>
<td>133 (49)</td>
<td>48 (45)</td>
<td>0.02</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The cerebral collateral cascade (CCC) comprises pial arterial collaterals defined by the Tan scale and venous outflow profiles determined by the Cortical Vein Opacification Score (COVES) on admission single-phase CT angiography images, and tissue-level collaterals determined by the hypoperfusion intensity ratio (HIR) derived from CT perfusion imaging. A favorable CCC (CCC+) profile was defined as: Tan ≥50%, HIR ≤0.4, COVES 3–6.

Statistical analysis was done using IBM SPSS statistics, v. 28.0 and SAS 9.4. 

**Patient demographics and presentation details**
CCC+ patients were younger (median [IQR] 72 years [61–80]) than CCCmixed (75 years [64–83]) and CCC− patients (77 years [68–83]) (P=0.002) and had lower presentation NIHSS scores (median [IQR] 10 [6–14]) compared with CCCmixed (15 [10–19]) and CCC− (18 [15–21]) (P<0.001). Blood glucose on admission was slightly lower in CCC+ patients (median [IQR] 116 mg/dL [99–141]) compared with CCCmixed (122 mg/dL [105–153]) and CCC− patients (121 mg/dL [106–157]) (P=0.032). A greater proportion of CCC+ patients (61%) received treatment with intravenous alteplase compared with CCCmixed (49%) and CCC− (45%) patients. All other patient characteristics are displayed in table 1.

**Imaging characteristics and clinical outcomes**
Baseline imaging evaluation, CCC+ patients had the highest ASPECTS (median [IQR] 9 [8–10]) vs 8 [6–9] in CCCmixed and 6 [5–8] in CCC− patients; P<0.001), smaller estimated baseline ischemic core volumes (median [IQR] 0 mL [0–7] vs 13 mL [0–28] in CCCmixed and 44 [18–87] in CCC− patients; P<0.001), smaller penumbra volumes (Tmax >6 s delay) on perfusion imaging (median [IQR] 90 mL [58–130] vs 129 mL [75–171] in CCCmixed and 174 [25–229] in CCC− patients; P<0.001), and smaller final infarct volumes (median [IQR] 9 mL 109 [75–160] vs 90 [70–146] mL in CCCmixed and 110 [63–146] mL in CCC− patients; P<0.001).
Penumbra volumes, or blood glucose values. Compared with were excluded due to unknown presentation NIHSS, core and imbalances and predictors of ΔNWU. Fifty-in a general linear model, which was adjusted for baseline For the primary outcome analysis, 481 patients were included Assessment of the primary outcome (ΔNWU) Neuroimaging Table 2 Imaging and clinical outcomes

<table>
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<th>P value (diff between groups)</th>
<th>P value (trend test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPECTS, median (IQR)</td>
<td>9 (8–10)</td>
<td>8 (6–9)</td>
<td>6 (5–8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline ischemic core volume (CBF &lt;30%) (mL), median (IQR)</td>
<td>0 (0–7)</td>
<td>13 (0–28)</td>
<td>44 (18–87)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Penumbra volume (Tmax &gt;6 s) (mL), median (IQR)</td>
<td>90 (58–130)</td>
<td>129 (75–171)</td>
<td>174 (125–229)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vessel occlusion location on CT angiography</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Internal carotid artery, n (%)</td>
<td>16 (10)</td>
<td>59 (22)</td>
<td>35 (33)</td>
<td></td>
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<tr>
<td>MCA one-segment occlusion, n (%)</td>
<td>98 (62)</td>
<td>172 (63)</td>
<td>65 (61)</td>
<td></td>
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<tr>
<td>MCA two-segment occlusion, n (%)</td>
<td>43 (27)</td>
<td>43 (16)</td>
<td>7 (7)</td>
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</tbody>
</table>

Ischemic lesion NWU estimates

NWU on admission NCCT (%), median (IQR) 2.42 (0.99–3.96) 6.54 (3.46–8.93) 8.38 (6.72–11.18) <0.001 <0.001

Follow-up imaging details

Final infarct volume (mL), median (IQR) 9 (4–20) 27 (10–67) 57 (25–139) <0.001 <0.001

Ischemic lesion edema assessment

CCC+ patients exhibited less median NWU on admission non-contrast head CT (median (IQR) 2.42% (0.99–3.96%)) compared with CCCmixed (6.54% (3.46–8.93%)) and CCC− (8.38% (6.72–11.18%)) (<0.001). In addition, the median ischemic lesion NWU at follow-up was lower in CCC+ patients (median (IQR) 6.94% (3.87–9.38%)) compared with patients with CCCmixed (13.94% (7.75–18.58%)) and CCC− (16.66% (11.20–22.96%)) (<0.001) profiles. Finally, the ischemic lesion edema growth (ΔNWU) measured at patient admission and after EVT treatment was found to be significantly lower in patients with a CCC+ profile (median (IQR) 3.88% (2.80–5.55%)) vs patients with CCCmixed (7.01% (4.01–9.99%)) and unfavorable CCC− profiles (8.51% (5.25–11.21%)) (<0.001) (table 2, figure 1).

Assessment of the primary outcome (ΔNWU)

For the primary outcome analysis, 481 patients were included in a general linear model, which was adjusted for baseline imbalances and predictors of ΔNWU. Fifty-seven patients were excluded due to unknown presentation NIHSS, core and penumbra volumes, or blood glucose values. Compared with patients with CCC+ profiles, CCC− (β 1.99, 95% CI 0.68 to 3.30, P=0.003) and CCCmixed (β 1.65, 95% CI 0.75 to 2.56, P<0.001) profiles were independently associated with higher

4 (20 to 27 mL (10–67) in CCCmixed and 57 mL (25–139) in CCC−). CCC+ patients were less likely to have a more proximal vessel occlusion compared with CCCmixed and CCC− patients (P<0.001).

CCC+ patients had more favorable functional outcomes on the modified Rankin Scale (mRS) 90 days after successful EVT treatment (median (IQR) mRS 1 (0–2)) compared with CCCmixed (4 (1–5)) and CCC− (5 (4–6)) (<0.001) patients (table 2).

Ischemic lesion edema assessment

CCC+ patients exhibited less median NWU on admission non-contrast head CT (median (IQR) 2.42% (0.99–3.96%)) compared with CCCmixed (6.54% (3.46–8.93%)) and CCC− (8.38% (6.72–11.18%)) (<0.001). In addition, the median ischemic lesion NWU at follow-up was lower inCCC+ patients (median (IQR) 6.94% (3.87–9.38%)) compared with patients with CCCmixed (13.94% (7.75–18.58%)) and CCC− (16.66% (11.20–22.96%)) (<0.001) profiles. Finally, the ischemic lesion edema growth (ΔNWU) measured at patient admission and after EVT treatment was found to be significantly lower in patients with a CCC+ profile (median (IQR) 3.88% (2.80–5.55%)) vs patients with CCCmixed (7.01% (4.01–9.99%)) and unfavorable CCC− profiles (8.51% (5.25–11.21%)) (<0.001) (table 2, figure 1).

Assessment of the primary outcome (ΔNWU)

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ischemic edema growth ($\Delta$NWU) in AIS-LVO patients who were successfully treated by endovascular thrombectomy, after controlling for blood glucose, age, presentation NIHSS, baseline ASPECTS, vessel occlusion localization, penumbra, and ischemic core volume. However, when comparing patients with a CCCmixed and CCC− profile, we did not find any difference in association with $\Delta$NWU for these respective patients ($\beta = -0.34$, 95% CI = −1.40 to 0.72, $P=0.532$) (table 3). Online supplemental figures 2 and 3 demonstrate patient examples for distinct CCC profiles.

Assessment of the secondary outcome (mRS 0–2)

For the secondary outcome analysis, 468 patients were included in a multivariable binary logistic regression model (online supplemental table 1). We included the same covariables as in the primary outcome model with the addition of $\Delta$NWU as independent variable. We found that an increase in $\Delta$NWU was independently associated with less odds of functional independence at 90 days (OR 0.74, 95% CI 0.68 to 0.72, $P<0.001$). In addition, we found that patients with more favorable collateral blood flow to and through ischemic tissue, as reflected by the CCC model, had higher odds for achieving good functional outcomes after successful thrombectomy treatment. Compared with CCC− (OR 1.33, 95% CI 4.88 to 36.76, $P<0.001$) and CCCmixed (OR 4.55, 95% CI 2.33 to 8.33, $P<0.001$) profiles, we found that CCC+ profiles were independently associated with good functional outcomes 90 days after successful endovascular treatment. Interestingly, patients who exhibited CCCmixed profiles still had higher odds of achieving good functional outcomes when compared with patients with CCC− profiles (OR 3.00, 95% CI 1.26 to 7.14, $P=0.01$).

**DISCUSSION**

In this study, we determined whether comprehensive assessment of cerebral collateral status is associated with ischemic lesion edema growth in AIS-LVO patients successfully treated with thrombectomy. Comprehensive cerebral collateral blood flow was assessed using the CCC framework and we evaluated the impact of different collateral profiles on quantitative ischemic lesion NWU changes between patient admission and follow-up ($\Delta$NWU) and clinical outcomes. We found that CCC+ patients developed less ischemic brain edema growth after successful thrombectomy compared with CCC− and CCCmixed patients. More favorable CCC profiles and decreased $\Delta$NWU were independently associated with functional independence 90 days after treatment. Our findings suggest that unhampered collateral blood flow from pial arteries through microvascular tissue-level vessels into draining cerebral cortical veins reflects robust cerebral microperfusion during brain ischemia, which is directly associated with less ischemic damage to the brain.9 27

Our findings have important implications for AIS-LVO patients eligible for EVT. A substantial proportion of AIS-LVO patients still exhibit poor clinical outcomes despite timely and successful vessel reperfusion.2 28–31 Besides other parameters, extensive ischemic brain edema formation is a known cause of poor clinical outcomes despite successful reperfusion.5 8 Our findings indicate that CCC− and CCCmixed patients are at an increased risk of brain edema progression, which may result in less favorable functional outcomes. Therefore, new treatments designed to reduce brain edema progression may be optimally tested in these patients.

NWU in ischemic tissue can be directly quantified as an imaging biomarker of ischaemic edema.12 While NWU assessment is currently still predominantly used in a research environment, this technique illustrates a well-understood and important pathophysiological phenomenon, namely brain edema development by compromised water hemostasis in ischemic brain tissue.13 Brain edema biology is complex and governed by multiple mechanisms associated with impaired cerebral tissue microperfusion.14 27 32 33 In addition, aggravated brain edema increases the risk for malignant infarction, which is associated with poor outcomes.12 Over time, extensive brain edema itself impairs microvascular blood flow and prior studies have demonstrated a strong link between hampered collateral blood flow and aggravated edema formation in AIS-LVO patients.10 11 14 While the extent of tissue edema can be directly quantified by means of quantitative NWU, several different ways exist to quantify collateral vessels on radiological imaging.18 One major drawback of many conventional collateral scores is that these approaches are only able to assess a minor proportion of the collateral circuit, thus they are unable to provide comprehensive assessment of collateral blood flow. However, critical patterns of cerebral hypoperfusion are likely reflected by the most distal arteries and their subsequent venous drainage, which are typically not determined by conventional collateral scores.24

The recent introduction of the CCC framework provides a comprehensive collateral vessel assessment in AIS-LVO patients.
A previous study found that a multiparametric evaluation of the collateral status during endovascular treatment triage was strongly associated with radiological and long-term clinical outcomes compared with a single-parameter approach alone, which is in line with our findings. However, the aforementioned study also included patients with unsuccessful vessel reperfusion status (TICI 0-2a) after thrombectomy and did not assess brain edema formation. The findings of this study suggest that hampered comprehensive collateral blood flow may result in aggravated brain edema despite successful vessel reperfusion, which likely promotes the exhibition of poor functional outcomes in this group of patients. Brain edema development represents one of the pathophysiological hallmarks of ischemic stroke pathophysiology and is inherently linked to clinical outcomes and neurological recovery. In addition, the individual collateral status has strong implications for maintaining microvascular blood flow during AIS-LVO, thus indirectly affecting cerebral water hemostasis. Consequently, our study provides an important link between edema development and collateral blood flow status. As brain edema formation and collateral blood flow are both linked to early clinical recovery and long-term functional outcomes after mechanical thrombectomy, a deeper knowledge and proper assessment of these parameters would provide important information to neurointerventionalists and physicians alike before and after treatment.

Interestingly, other studies found that the components of the CCC model were associated with early edema progression (defined as estimated edema growth from the time of symptom onset to patient admission) and the magnitude of edema formation after thrombectomy. While one study did not find a significant association between pial arterial collaterals and edema formation after treatment, others reported a strong correlation between arterial collaterals and edema development over time. Another study found a strong link between tissue-level collaterals and venous outflow profiles with respect to clinical outcomes in patients treated by thrombectomy. However, differences in the aforementioned findings may result from the use of different collateral scores for pial arterial collateral assessment, different patient characteristics and treatment protocols. In addition, it is important to note that large infarcts do not necessarily have higher ischemic lesion NWU measures and vice versa. In particular, also small infarcts can exhibit elevated NWU percentages indicating more severe tissue damage, which may lead to worse clinical outcomes despite smaller infarct volumes. However, this mechanism is still not well understood and requires additional research. Further prospective studies are needed to investigate the impact of distinct collateral profiles on patient outcomes and thrombectomy efficacy in more detail. Finally, to date, a comprehensive collateral assessment using the CCC model is time consuming. Thus, an automated approach to determine the vasculature of the CCC model would hold appeal.

Our study has limitations. The retrospective design may introduce bias and limit the generalizability of our findings. Although we only included patients with complete opacification of the sigmoid sinuses, the potential technical limitations for the use of single-phase CT angiography images to determine venous outflow have been discussed before. The use of other imaging scores to determine pial arterial collaterals and utilization of different processing software to determine perfusion imaging derived parameters may have led to different results.

In conclusion, in AIS-LVO patients, a comprehensive assessment of the collateral status using the CCC model is strongly associated with ischemic lesion NWU development determined between patient admission and 24–48 hours after successful thrombectomy treatment. This study highlights the importance of a more holistic approach towards collateral blood flow assessment in AIS-LVO patients, and elucidates the crucial role of unhampered cerebral collateral blood flow with regards to cerebral edema formation in ischemic brains.
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Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data that supported our work will be available from the corresponding author upon reasonable request.

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Supplemental Material

Brain Edema Growth after Thrombectomy is associated with Comprehensive Collateral Blood Flow

Supplemental Figure 1. Patient Flow Chart

CCC: Cerebral Collateral Cascade; NWU: Net Water Uptake; ICA: Internal Carotid Artery; M1: First segment of the middle cerebral artery; M2: Second segment of the middle cerebral artery; CT: Computed Tomography; TICI: Thrombolysis in Cerebral Infarction.
Supplemental Figure 2. Patient Example

Patient with an acute ischemic stroke of the left media territory due to an occlusion of the first segment of the middle cerebral artery (M1). These images demonstrate a patient with a favorable cerebral collateral cascade (CCC) profile and comparatively low ischemic lesion edema growth between admission and follow-up imaging after successful thrombectomy treatment. Image A shows an admission axial non-contrast head Computed Tomography image on which the area of early infarct hypoattenuation was outlined (red area). Density measures were acquired from this area in order to determine ischemic lesion net water uptake values by comparison to the unaffected contralateral hemisphere (green area). In this case, a net water uptake of 3.4% was measured in image A. Images B1-B3 exemplify the determination of the components of the CCC model. Pial arterial collaterals were scored in image B1 on single-phase CT angiography and good arterial collaterals are marked by the green arrows. A hypoperfusion intensity ratio of 0.3 was automatically calculated from perfusion imaging indicating favorable tissue-level collaterals (B2). The tissue-at-risk is displayed by the distinct Tmax values on color-coded perfusion output maps. Image B3 exemplifies a favorable venous outflow (Cortical Vein Opacification Score of 2) determined within the vein of labbé (dotted green arrow) of the left hemisphere. Image C demonstrates the ischemic lesion net water uptake measurement (6.2%) 31 hours after thrombectomy treatment, similar to the approach described above. The estimated ischemic lesion edema growth between admission and follow-up imaging was 2.8%. The patient exhibited a good functional outcome (modified Rankin Scale score of 1) 90-days after treatment.
Supplemental Figure 3. Patient Example 2

Patient in their 50s with acute ischemic stroke due to a right-sided occlusion of the middle part of the first segment of the middle cerebral artery (M1). This image demonstrates an example for an unfavorable collateral profile as determined by the cerebral collateral cascade (CCC) model. Image A shows a baseline axial non-contrast head Computed Tomography image on the level of the basal ganglia. Density measures were acquired from the outlined area in red to determine ischemic lesion net water uptake values in comparison to a mirrored region of interest from the unaffected contralateral brain tissue (green area). Please note that areas including cerebrospinal fluid (e.g. around the insula cortex) were excluded from the measurement, which is not displayed for the sake of clarity. Net water uptake in image A was measured at 5.4%. Images B1-B3 exemplify the determination of the components of the CCC model. Pial arterial collaterals were scored in image B1 on single-phase CT angiography and poor (absent) pial arterial collaterals are marked by the red arrows. A hypoperfusion intensity ratio of 0.7 was automatically calculated from perfusion imaging indicating unfavorable tissue-level collaterals (B2). The tissue-at-risk is displayed by the distinct Tmax values on color-coded perfusion output maps. Image B3 exemplifies absence of venous outflow (Cortical Vein Opacification Score of 0) determined in the vein of labbé (dotted red arrow) of the affected right hemisphere. Ischemic lesion net water uptake after successful thrombectomy treatment was 15.4% (C). Consequently, ischemic lesion edema growth (Δ net water uptake) between admission and follow-up imaging was ~10%. This patient exhibited an unfavorable neurological outcome 90-days after thrombectomy treatment (modified Rankin Scale score of 4).
Supplemental Table 1: Secondary Outcome Analysis (mRS 0-2) – Binary Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Predictors</th>
<th>aOR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCC overall</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCC+ versus CCC-</td>
<td>13.39</td>
<td>4.88-36.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCC&lt;sub&gt;mixed&lt;/sub&gt; versus CCC+</td>
<td>0.22</td>
<td>0.12-0.43</td>
<td>&lt;0.001</td>
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<tr>
<td>CCC&lt;sub&gt;mixed&lt;/sub&gt; versus CCC-</td>
<td>3.00</td>
<td>1.26-7.14</td>
<td>0.01</td>
</tr>
<tr>
<td>NWU delta</td>
<td>0.74</td>
<td>0.68-0.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood Glucose, per 10 units, mg/dl</td>
<td>0.94</td>
<td>0.89-0.999</td>
<td>0.04</td>
</tr>
<tr>
<td>Age, per 5 years</td>
<td>0.90</td>
<td>0.82-0.98</td>
<td>0.20</td>
</tr>
<tr>
<td>Presentation NIHSS</td>
<td>0.88</td>
<td>0.84-0.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ASPECTS</td>
<td>1.06</td>
<td>0.91-1.24</td>
<td>0.45</td>
</tr>
<tr>
<td>Penumbra Volume, per 5 ml</td>
<td>0.98</td>
<td>0.93-1.03</td>
<td>0.004</td>
</tr>
<tr>
<td>Core Volume, per 5 ml</td>
<td>0.01</td>
<td>-0.01-0.02</td>
<td>0.41</td>
</tr>
<tr>
<td>Vessel Occlusion Localization</td>
<td></td>
<td></td>
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<tr>
<td>M2 versus ICA</td>
<td>1.29</td>
<td>0.49-3.40</td>
<td>0.61</td>
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<tr>
<td>M1 versus M2</td>
<td>0.80</td>
<td>0.38-1.66</td>
<td>0.54</td>
</tr>
<tr>
<td>M1 versus ICA</td>
<td>1.03</td>
<td>0.48-2.22</td>
<td>0.94</td>
</tr>
</tbody>
</table>

*Number of events included into this analysis=468. Seventy patients were excluded from this analysis due to unknown presentation National Institutes of Health Stroke Scale values, due to unknown blood glucose values or unknown status of functional independence 90-days after treatment.

Legend: NIHSS = National Institutes of Health Stroke Scale; ASPECTS = Alberta Stroke Program Early CT Score; OR = Odds Ratio, CI = Confidence Interval; CBF = Cerebral Blood Flow; NWU = Net Water Uptake, ICA = Internal Carotid Artery, M1/M2 = First or second segment of the middle cerebral artery.

CCC = Cerebral Collateral Cascade. The CCC comprises pial arterial collaterals defined by the Tan scale and venous outflow profiles determined by the Cortical Vein Opacification Score on admission single-phase CT angiography.
images, and tissue-level collaterals determined by the hypoperfusion intensity ratio derived from CT perfusion imaging.

A favorable CCC (CCC+) profile was defined as: Tan ≥50%, Hypoperfusion Intensity Ratio ≤0.4, cortical vein opacification score of 3-6.

An unfavorable CCC (CCC-) profile was regarded as: Tan <50%, Hypoperfusion Intensity Ratio >0.4, and cortical vein opacification score of 0-2.

CCCmixed profiles were assigned to patients, who did not fulfill the criteria of the CCC+ or CCC- groups.