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ABSTRACT

BACKGROUND AND PURPOSE: Information of collateral flow may help to determine eligibility for thrombectomy. Our aim was to identify CT perfusion–based surrogate parameters of good collateral status in acute anterior circulation ischemic stroke.

MATERIALS AND METHODS: In this retrospective study, we assessed the collateral status of 214 patients who presented with acute ischemic stroke due to occlusion of the MCA M1 segment or the carotid terminus. Collaterals were assessed on dynamic CTA images analogous to the multiphase CTA score by Menon et al. CT perfusion parameters (time-to-maximum, relative CBF, hypoperfusion intensity ratio, and CBV-index) were assessed with RAPID software. The Spearman rank correlation and receiver operating characteristic analyses were performed to identify the parameters that correlate with collateral scores and good collateral supply (defined as a collateral score of ≥4).

RESULTS: The Spearman rank correlation was highest for a relative CBF < 38% volume ($\rho = -0.66$, $P < .001$), followed by the hypoperfusion intensity ratio ($\rho = -0.49$, $P < .001$), CBV-index ($\rho = 0.51$, $P < .001$), and time-to-maximum > 8 seconds ($\rho = -0.54$, $P < .001$). Good collateral status was better identified by a relative CBF < 38% at a lesion size <27 mL (sensitivity of 75%, specificity of 80%) compared with a hypoperfusion intensity ratio of <0.4 (sensitivity of 75%, specificity of 62%), CBV-index of >0.8 (sensitivity of 60%, specificity of 78%), and time-to-maximum > 8 seconds (sensitivity of 68%, specificity of 76%).

CONCLUSIONS: Automated CT perfusion analysis allows accurate identification of collateral status in acute ischemic stroke. A relative CBF < 38% may be a better perfusion-based indicator of good collateral supply compared with time-to-maximum, the hypoperfusion intensity ratio, and the CBV-index.

ABBREVIATIONS: AUC = area under the curve; HIR = hypoperfusion intensity ratio; IQR = interquartile range; mCTA = multiphase CTA; rCBF = relative CBF; sCTA = single-phase CTA; Tmax = time-to-maximum

According to the latest guidelines of the American Stroke Association, information on collateral flow may help to determine eligibility for mechanical thrombectomy in some candidates.[1] Although a multitude of different methods and collateral grading systems have been described,[2] the guidelines do not recommend a specific method. In CT imaging, collaterals can be assessed on single-phase or multiphase CT angiography. Single-phase CTA (sCTA) collateral scores may underestimate the collateral supply because they rely on the spatial extent of collateral enhancement during a single phase only. In contrast, multiphase CTA (mCTA) or dynamic CTA, which is postprocessed from CTP data, provides information on both the spatial extent and delay in collateral filling.[3-5] In the past, collateral grading based on mCTA was found to predict final infarct volume and clinical outcome better than sCTA-based collateral assessment.[4,6]

In recent years, various methods of automated assessment of collateral status have been proposed.[7,8] Lee et al,[9] for instance, reported that the perfusion delay, as indicated by the time-to-maximum (Tmax) parameter, correlates with sCTA collateral status. Furthermore, novel perfusion-based parameters, such as the hypoperfusion intensity ratio (HIR) and the CBV-index were introduced.[10-12] The HIR is calculated by dividing the volume of tissue with a perfusion delay of Tmax > 10 seconds by the volume of tissue with Tmax > 6 seconds. The CBV-index indicates the

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mean CBV within the volume of tissue with a perfusion delay of Tmax > 6 seconds divided by the mean CBV of healthy tissue.[10,13] These parameters were found to correlate with infarct growth during interhospital transfer for thrombectomy[14] and with clinical outcome after thrombectomy.[13] Whether the HIR or CBV-index identifies collateral status better than other perfusion parameters remains to be investigated.

The aim of this study was, therefore, to identify and compare CTP-based surrogate parameters (Tmax, CBF, HIR, and CBV-index) of collateral supply on dynamic CTA.

MATERIALS AND METHODS

Patient Data

At our comprehensive stroke center, all patients transferred to the angiography suite for thrombectomy are registered in a prospective institutional registry. This registry was screened retrospectively for patients with an occlusion of the carotid terminus or the M1 segment of the MCA and acquisition of volume CTP between April 2014 and March 2020. The study was approved by the local ethics board of Heidelberg University, and informed consent was waived.

CTP Imaging

CTP imaging was performed on a 64-multislice CT (Somatom Definition AS; Siemens) with a z-axis coverage of 8 cm. A contrast bolus of 36 mL of iobitridol (Xenetix 350; Guerbet) followed by a saline flush of 20 mL was applied at a flow rate of 6.0 mL/s. Acquisition parameters for CTP were 80 kV and 180 mAs, and acquisition duration was 44 seconds at a repetition rate of 1.5 seconds. CTP data were reconstructed with a section thickness of 5 mm.[8]

Perfusion Analysis

Fully automated perfusion analysis was performed using RApid processing of PerfusIon and Diffusion (RAPID software, Version 5.0.4; iSchemaView). The volumes with Tmax > 6 seconds, > 8 seconds, > 10 seconds; the volumes with relative CBF (rCBF) < 30%, < 34%, < 38% (as predefined in the RAPID software reports); and the HIR and CBV-index were analyzed. When patients had no lesions with Tmax > 6 seconds, the HIR and CBV-index were undefined by RAPID. In these cases, the HIR and CBV-index were set to 0 and 1.0, respectively.

Assessment of Dynamic CTA Collateral Status

CTP images were postprocessed using syngo.CT Dynamic Angio (Siemens Healthcare, Erlangen, Germany).[15] First, an arterial input function and a venous output function were defined by manually placing ROIs within an arterial vessel in the unaffected hemisphere and within a vein or dural sinus. Analogously to Menon et al,[4] 3 phases were determined. CTA images of the arterial phase were then created by MIP of the temporal volumes ± 2 seconds from the peak of the arterial input function, whereas CT images of the venous phase were created by temporal MIP of the acquisitions ± 2 seconds from the peak of the venous output function. CTA images for a late venous phase were created by temporal MIP of the acquisitions 6–12 seconds after the venous peak. Therefore, dynamic CTA phases were comparable with conventional multiphase CTA as described by Menon et al,[4] in which arterial, venous, and late venous CTA images were acquired 8 seconds apart with an acquisition time for each volume of 3.6 seconds.[4]

Collateral status on dynamic CTA was assessed by an experienced reader who was blinded to clinical data and perfusion analysis. Collaterals were scored analogous to the mCTA collateral scoring system by Menon et al[4] using a 6-point ordinal scale (ranging from absent collateral supply [collateral sore = 0] to excellent collateral supply [score = 5]). Good collaterals were defined as collateral scores of 4–5 (Fig 1).[3,4]

Statistical Analysis

Statistical analysis was performed with R statistical and computing software (http://www.r-project.org). Group differences were assessed by the Fisher exact test for nominal variables and the Mann-Whitney *U* test for continuous variables. Correlation between perfusion indices and collateral scores was assessed by the Spearman rank correlation. Receiver operating characteristic curves were analyzed for the identification of good collaterals (scores = 4–5). Differences of the area under the curve (AUC) were assessed by the DeLong test.[16] Optimal thresholds to identify good collateral status were chosen according to the Youden index. The statistical significance level was set to $P < .05$. Medians are provided with their interquartile range (IQR), and means, with their SDs. All confidence intervals are provided as 95% CI.

RESULTS

Baseline Patient Characteristics

Two-hundred thirty-seven patients met the inclusion criteria. Of these, 1 patient had to be excluded due to an incomplete perfusion acquisition. Six patients were excluded from the analysis due to severe head motion during image acquisition, and 16 patients were excluded due to bolus delay or insufficient contrast enhancement. In all cases included in the analysis, the first pass of the contrast agent bolus was captured completely. Furthermore, 1 patient with an acute space-occupying subdural hematoma was excluded because the RAPID software falsely classified the hematoma as an infarct core.

Altogether, collateral scores and CTP analyses of 214 patients (122 women, 57%) were included in the analysis. In all cases, the first pass of contrast bolus was completely captured. The occlusion site was the MCA M1-segment in 169 (79%) patients and the carotid terminus in 45 (21%) patients. The median time from symptom onset or last seen well to imaging was 187 minutes (IQR, 96–364 minutes). The median NIHSS score at admission was 16 (IQR, 11–20), and the median ASPECTS on acute CT imaging was 9 (IQR, 7–10). Baseline patient characteristics are summarized in the Online Supplemental Data.

Collateral Scores and Perfusion Indices

The collateral score was 0 in 6 patients (3%), 1 in 16 patients (7%), 2 in 26 patients (12%), 3 in 55 (26%) patients, 4 in 58 (27%) patients, and 5 in 53 (25%) patients.

The mean infarct core (rCBF < 30%) was 24 mL (95% CI 19–28 mL) and mean lesion size of Tmax > 6 seconds was 111 mL (95% CI 102–119 mL). The mean CBV-index was 0.68 (95% CI

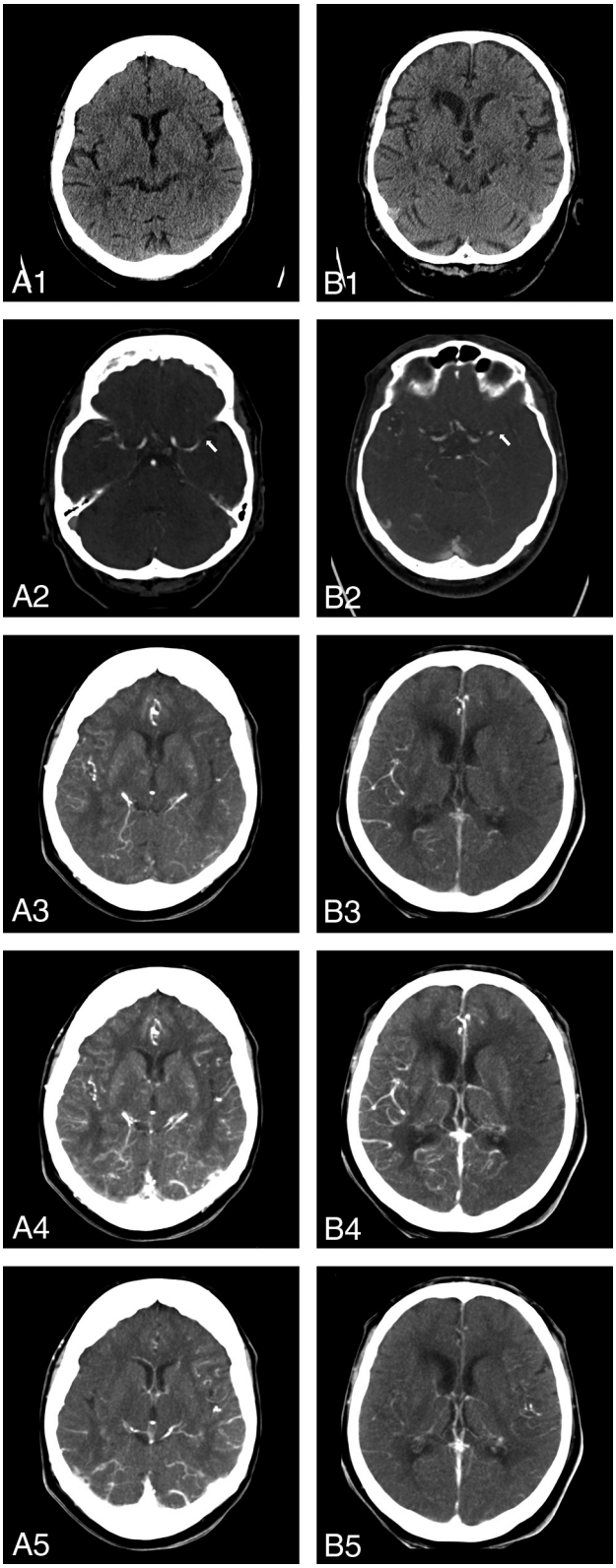

FIG 1. Noncontrast CT, conventional CTA, and dynamic CTA for 2 exemplary patients with acute ischemic stroke. Patient A (*left column*) underwent imaging within 293 minutes from symptom onset, and patient B (*right column*), within 284 minutes from symptom onset. Both patients had an ASPECTS of 10 on noncontrast CT (subfigures *A1* and *B1*). Conventional CTA reveals an acute occlusion of the M1 segment of the left MCA (indicated by the *arrows* on subfigures *A2* and *B2*) for both patients. On dynamic CTA, patient A had good collateral supply, and arterial contrast-enhancement was almost synchronous, compared with the unaffected right hemisphere (early arterial phase [*A3*]; parenchymal phase [*A4*]; late venous phase [*A5*]). In contrast, patient B exhibited poor collateral supply on dynamic CTA with delayed and reduced arterial enhancement (reduced and delayed contrast-enhancement by 2 phases compared with the contralateral hemisphere [*B3–B5*]).

0.65–0.70), and the mean HIR was 0.37 (95% CI 0.34–0.40). In 4 patients (2%), a lesion size of Tmax > 6 seconds was 0 mL; therefore, the RAPID software was unable to calculate the HIR and CBV-index. These parameters were set manually to HIR = 0 and CBV-index = 1.0.

On a group level, all perfusion parameters differed significantly between patients with good-versus-poor collaterals ($P < .001$; Table 1 and Fig 2). Furthermore, all perfusion indices correlated directly with collateral scores on the Spearman rank correlation analysis (Table 2). The highest (negative) correlation was found for volumes with rCBF < 38%, followed by Tmax > 8 seconds, CBV-index, and HIR.

Receiver operating characteristic analysis for good collateral status revealed similar results (Fig 3). With an AUC of 0.83, rCBF performed the best (Table 2). There were significant differences in the AUC between rCBF < 38% and Tmax > 6 seconds ($P = .01$), Tmax > 8 seconds ($P = .04$), Tmax > 10 seconds ($P = .02$), CBV-index ($P = .008$), and HIR ($P < .001$), respectively. According to the Youden index, good collateral status was identified on rCBF < 38% maps when the lesion size was <27 mL (sensitivity of 75%, specificity of 80%, and accuracy 77%) and the resulting contingency table was significant ($P < .001$; Table 3).

DISCUSSION

The aim of this study was to identify CTP-based surrogate parameters of collateral supply. We found that all CTP parameters, particularly Tmax delay, CBF lesion size, CBV-index, and HIR, correlated with collateral supply. The highest correlation was observed for rCBF < 38%.

Compared with previous studies, our study confirms that the HIR and CBV-index correlate well with collateral status. We found that HIR <0.4 identifies good collateral status with a sensitivity of 75% and specificity of 62%. Guenego et al[11] reported a sensitivity of 79% and specificity of 56% for the same threshold. Lyndon et al[17] compared the HIR with mCTA collateral status in 52 patients and found an optimum cutoff value of HIR >0.45 to identify poor collateral status.

However, the comparison of HIR, CBV-index, Tmax, and CBF in our study revealed that CBF, particularly the volume with rCBF < 38%, may be an even better predictor of good collateral status. In our analysis, good collateral supply was identified best by a volume with rCBF < 38% of <27 mL, with a sensitivity of 75% at a specificity of 80%.

Noticeably, the RAPID software uses rCBF for the identification of the ischemic core as well, but at a threshold of rCBF < 30%. It additionally provides rCBF volumes with thresholds at 34% and 38%. So far, data analyzing and comparing the clinical relevance of these thresholds is scarce. Muehlen et al[18] reported

Table 1: CTP parameters in patients with good-versus-poor collaterals[a]

Perfusion Parameter	All Patients	Patients with Poor Collaterals (Score, 0–3)	Patients with Good Collaterals (Score, 4–5)	*P* Value
Tmax > 6 sec (mL)	111 (102–119)	135 (124–145)	88 (77–99)	<.001
Tmax > 8 sec (mL)	74 (67– 82)	97 (88–107)	53 (44–63)	<.001
Tmax > 10 sec (mL)	48 (43–54)	66 (58–74)	32 (25–39)	<.001
rCBF < 30%, mL	24 (19–28)	41 (33–49)	8 (5–11)	<.001
rCBF < 34%, mL	30 (25–35)	50 (41–58)	11 (8–14)	<.001
rCBF < 38%, mL	36 (31–42)	59 (50–68)	15 (12–19)	<.001
CBV-index	0.68 (0.65–0.70)	0.60 (0.56–0.63)	0.76 (0.72–0.78)	<.001
HIR	0.37 (0.34–0.40)	0.46 (0.42–0.50)	0.29 (0.24–0.33)	<.001

[a] Data are given as mean values and 95% confidence intervals.

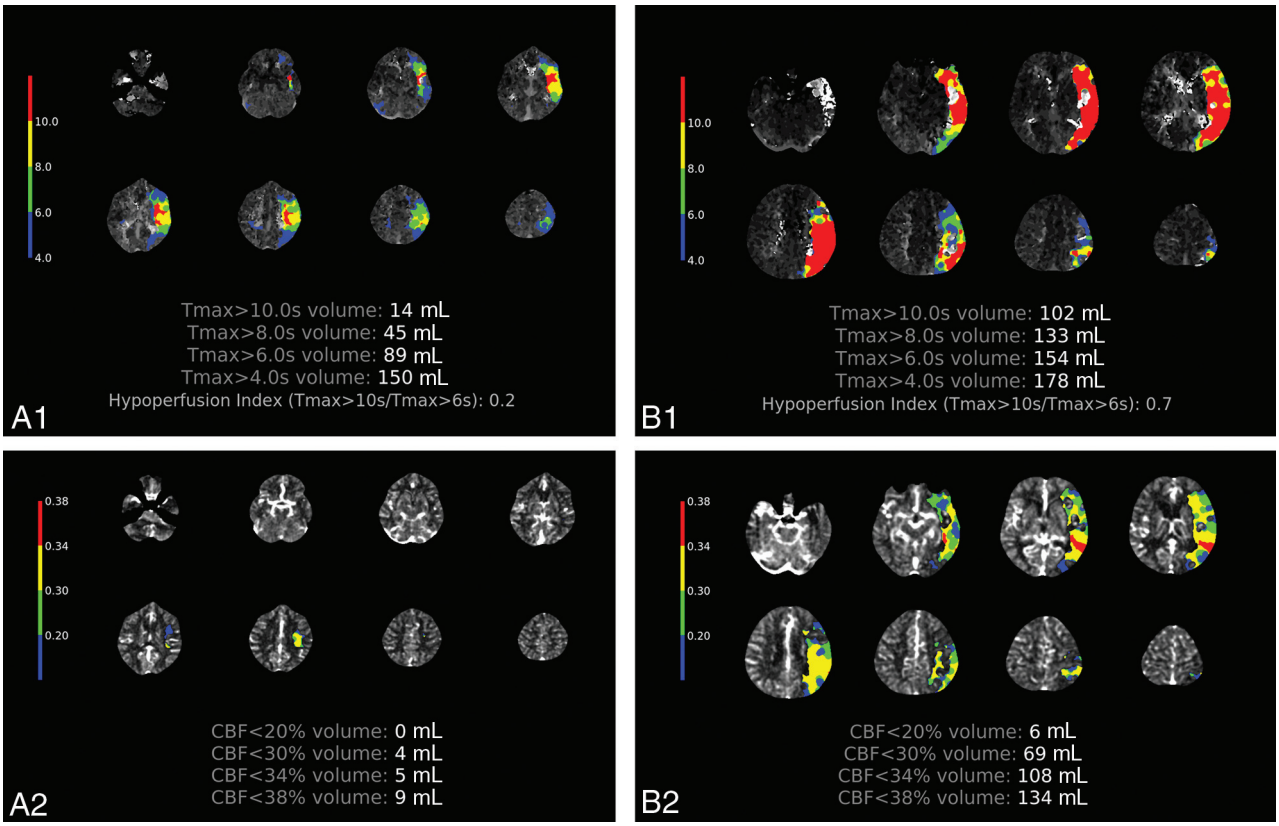

FIG 2. Tmax maps (*A1* and *B1*) and CBF maps (*A2* and *B2*) for 2 patients with either good (patient A, *left column*) or poor collateral supply (patient B, *right column*). Tmax lesion sizes, HIR, and CBF lesion sizes are all considerably smaller for patient A with good collateral supply compared with patient B with poor collateral supply. See Fig 1 for the corresponding noncontrast CT, CTA, and dynamic CTA for the same patients.

that rCBF < 38% correlates best with the final infarct volume. However, compared with a threshold of rCBF < 30%, it was associated with a higher risk of infarct overestimation.[18]

Taken together, our findings indicate a strong interaction between collateral status and infarct core size. CBF measures blood flow velocity, which is found to depend on collaterals in the case of an upstream occlusion. We found that an rCBF < 38% indicates poor collateral status best, while rCBF < 30% may be the critical threshold for an irreversible tissue injury.

The major strength of this study is the relatively large cohort size with 214 patients. Additionally, collateral scores were assessed on dynamic CTA images, accounting for both the spatial extent and the delay of collateral supply. None of the previous studies correlated HIR with collateral status assessed on dynamic CTA. Furthermore, we used the RAPID software, which is an established perfusion postprocessing tool, to determine the CTP parameters in this study.[19]

Thus, several factors such as bolus shape, scanner protocol, and generation and postprocessing software can influence CTP analysis. Moreover, CTP analysis is susceptible to patient-specific factors and head motion.[20] Compared with the drawbacks of collateral assessment on CTA, including the reduced temporal resolution and need for a visual assessment, quantitative collateral grading based on perfusion data may still allow a more uniform and systematic collateral assessment.

Further limitations result from the monocentric, retrospective study design. Due to this retrospective design, we could include only patients who were transferred to the angiography suite and registered in our institutional thrombectomy database. As a result,

Table 2: Results from the Spearman rank correlation analysis for collateral score as a function of perfusion parameters (ρ [95% CI] and *P* value) and from ROC analysis for the identification of good collateral status[a]

Perfusion Parameter	ρ (95% CI)	*P* Value	AUC (95% CI)	Cutoff Value	Sensitivity	Specificity	Accuracy
Tmax >6 sec (mL)	−0.50 (−0.61 to −0.39)	<.001	0.75 (0.68–0.81)[b]	124 mL	56%	82%	69%
Tmax >8 sec (mL)	−0.54 (−0.64 to −0.43)	<.001	0.77 (0.71–0.83)[b]	74 mL	68%	76%	72%
Tmax >10 sec (mL)	−0.50 (−0.60 to−0.39)	<.001	0.77 (0.71–0.83)[b]	53 mL	64%	80%	72%
rCBF < 30% (mL)	−0.61 (−0.71 to −0.52)	<.001	0.81 (0.75–0.87)	14 mL	72%	82%	77%
rCBF < 34% (mL)	−0.64 (−0.73 to −0–55)	<.001	0.83 (0.77–0.88)	25 mL	67%	87%	77%
rCBF < 38% (mL)	−0.66 (−0.74 to −0.57)	<.001	0.83 (0.78–0.89)	27 mL	75%	80%	77%
CBV-index	+0.51 (0.40–0.63)	<.001	0.76 (0.69–0.81)[b]	0.8	60%	78%	69%
HIR	−0.49 (−0.60−0.37)	<.001	0.73 (0.66–0.79)[b]	0.4	75%	62%	65%

[a] Overall, the volume with an rCBF < 38% performed best. Optimal cutoff values to identify good collateral supply were estimated according to the Youden index.
[b] Significant differences in AUC compared with the AUC for the volume with rCBF < 38%.

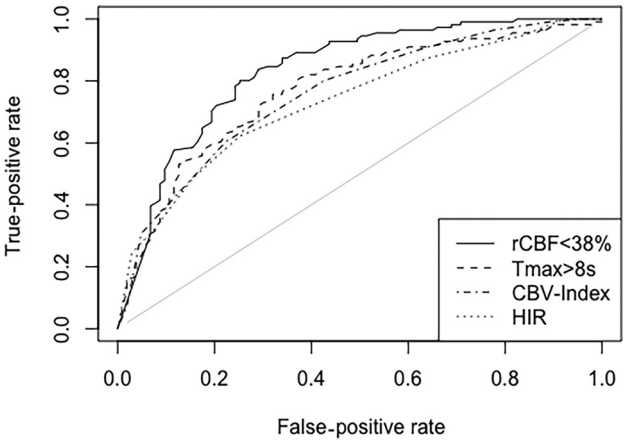

FIG 3. Receiver operating characteristics for rCBF < 38% (*solid line*), Tmax > 8 seconds (*dashed line*), the CBV-index (*dot-dashed line*), and HIR (*dotted line*) for the identification of good collateral status. The AUC was highest for rCBF < 38% with an AUC of 0.83.

Table 3: Contingency table for collateral status compared with volume with rCBF < 38%[a]

Volume with rCBF <38%: Collateral Status	<27 mL	≥27 mL	Total
Good collateral status (score 4–5)	89	22	111
Poor collateral status (score 0–3)	26	77	103
Total	115	99	214

[a] Good collateral status was significantly associated with a smaller rCBF < 38% lesion size (Fisher exact test was significant with $P < .001$).

there is a potential selection bias toward patients with better collateral status and smaller infarct sizes. Only 10% of the patients showed absent or nearly absent collaterals (scores = 0–1). Nonetheless, the proportion of patients with poor collaterals (48% with scores of 0–3) was higher compared with other studies such as that of Lyndon et al.[17] Therefore, a potential selection bias should not affect the validity of the results.

Another minor limitation is the absence of a collateral score based on DSA, which is still considered the criterion standard for collateral assessment. Depending on the occlusion location and the anatomy of the circle of Willis, however, DSA may underestimate collateral supply unless images from the contralateral ICA and vertebral artery are obtained. Collateral scoring and perfusion parameters are based on the same source data in our study, which could be regarded as a limitation.

CONCLUSIONS

Automated CTP analysis allows accurate identification of collateral supply in acute ischemic stroke. The volume of rCBF < 38% may be a more precise perfusion-based indicator of good collateral status than Tmax, HIR, or CBV-index.

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