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ABSTRACT

BACKGROUND AND PURPOSE: Collateral status and thrombus length have been independently associated with functional outcome in patients with acute ischemic stroke. It has been suggested that thrombus length would influence functional outcome via interaction with the collateral circulation. We investigated the individual and combined effects of thrombus length assessed by the clot burden score and collateral status assessed by a FLAIR vascular hyperintensity–ASPECTS rating system on functional outcome (mRS).

MATERIALS AND METHODS: Patients with anterior circulation acute ischemic stroke due to large-vessel occlusion from the ASTER and THRACE trials treated with endovascular thrombectomy were pooled. The clot burden score and FLAIR vascular hyperintensity score were determined on MR imaging obtained before endovascular thrombectomy. Favorable outcome was defined as an mRS score of 0–2 at 90 days. Association of the clot burden score and the FLAIR vascular hyperintensity score with favorable outcome (individual effect and interaction) was examined using logistic regression models.

RESULTS: Of the 326 patients treated by endovascular thrombectomy with both the clot burden score and FLAIR vascular hyperintensity assessment, favorable outcome was observed in 165 (51%). The rate of favorable outcome increased with clot burden score (smaller clots) and FLAIR vascular hyperintensity (better collaterals) values. The association between clot burden score and functional outcome was significantly modified by the FLAIR vascular hyperintensity score, and this association was stronger in patients with good collaterals, with an adjusted OR = 6.15 (95% CI, 1.03–36.81).

CONCLUSIONS: The association between the clot burden score and functional outcome varied for different collateral scores. The FLAIR vascular hyperintensity score might be a valuable prognostic factor, especially when contrast-based vascular imaging is not available.

ABBREVIATIONS: AIS = acute ischemic stroke; CBS = clot burden score; EVT = endovascular thrombectomy; FVH = FLAIR vascular hyperintensity; IVT = intravenous thrombolysis; mTICI = modified TICI score

Therapeutic reperfusion with endovascular thrombectomy (EVT) is consistently associated with a better long-term functional outcome in anterior circulation acute ischemic stroke (AIS).[1] Early reperfusion is the mainstay of therapy because it strongly predicts functional outcome.[2] Many factors impact clinical outcomes, including the extent of clot and collateral supply.[3–7]

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The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Clinical Trial Registration: ClinicalTrials.gov Identifier NCT02523261 and NCT01062698.

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The clot burden score (CBS) assessed by the T2* MR imaging sequence (T2*-CBS), which was adapted from the CTA-CBS,[8] has been used to assess the extent of the clot[9] and has been independently associated with functional outcome in patients undergoing EVT.[10]

Good collaterals have been related to better clinical outcome through 2 distinct mechanisms. First, collaterals are thought to contribute to prolonged penumbra sustenance.[11,12] Second, good retrograde collateral filling beyond the occlusion could promote successful reperfusion by providing more access to thrombolytics at the distal end of the clot and robust collaterals dissolving clot fragments in the distal vasculature.[13,14] The Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration analysis suggested a benefit with EVT across all strata of collateral circulation status;[15] however, patients with poor collaterals are less likely to benefit from EVT than those with better collaterals.

Most interesting, FLAIR vascular hyperintensity (FVH) on baseline MR imaging could indicate the formation of a leptomeningeal collateral circulation and serve as a prognostic marker for patients with AIS.[16-18] Both collaterals and the CBS were separately associated with functional outcome in patients undergoing EVT,[10,16] but their combined effect regarding clinical outcome is still poorly understood and has been assessed and quantified only with CTA or contrast-enhanced MRA in patients with AIS.[14,15] Furthermore, the lack of adjustment for possible confounders because of the small number of patients with very low collateral scores might also have influenced results in these studies.

The purpose of this study was to determine whether there is an association between the CBS and FVH score and whether the association between the CBS and functional outcome is modified by the FVH score for patients who were treated by EVT for large-vessel occlusion within the framework of the Contact Aspiration versus Stent Retriever for Successful Revascularization (ASTER) and the THRombectomie des Artères CErebrales (THRACE) randomized trials.[19,20]

MATERIALS AND METHODS

Ethics and Data Availability Statement

The ASTER (ClinicalTrials.gov No. NCT02523261) and THRACE (ClinicalTrials.gov No. NCT01062698) protocols were approved by an independent institutional review board (Comité de Protection des Personnes Ile de France VI and Comité de Protection des Personnes III Nord Est Ethics Committee, respectively) and the research boards of the participating centers. All patients or their legal representatives provided written informed consent. This article has been prepared according to the Consolidated Standards Of Reporting Trials (CONSORT statement; http://www.consort-statement.org/). The data that support the findings of this study are available from the corresponding author on reasonable request and after clearance by the local ethics committees.

Study Design and Patient Selection

The designs of the 2 trials from which our study population is derived have already been reported.[19,20] Briefly, the ASTER study was designed to compare the effect of 2 first-line strategies for EVT (contact aspiration versus stent retriever use) on reperfusion rates at the end of endovascular procedures. Use of intravenous thrombolysis (IVT) was permitted. The THRACE trial aimed to compare IVT alone with IVT plus EVT using a stent retriever to determine their effects on clinical independence at 3 months in patients with AIS caused by large-vessel occlusion.

We included patients screened by MR imaging as a first-line imaging triage from the ASTER trial (between October 2015 and October 2016) and from the THRACE trial (patients who received IVT plus EVT as a first-line strategy between June 2010 and February 2015). Patients with posterior circulation and tandem occlusion were excluded, as were patients for whom baseline FVH information was not available because of motion artifacts during imaging acquisition or because a 3D-FLAIR sequence was performed instead of axial 2D-FLAIR. The inclusion flow chart is presented in Online Fig 1. ASTER and THRACE did not use the CBS or collateral score as an imaging-selection criterion.[19,20]

Clinical and Imaging Assessment

Demographic and clinical data (including sex, age, history of hypertension, systolic and diastolic blood pressure, diabetes mellitus, dyslipidemia, glycemia, smoking habits, initial NIHSS score, IVT use, and time metrics) were extracted from the ASTER and THRACE data bases.

For both trials, all neuroimaging data were stored centrally and reanalyzed by a central imaging committee. All images and angiograms before and after EVT were reviewed by an independent committee of 2 experienced neuroradiologists who were blinded to the randomization group and patient clinical outcome. Discordance was resolved in consensus.

Baseline DWI-ASPECTS and occlusion site (either the M1 or M2 segment of the MCA or ICA) were also recorded. Reperfusion status was assessed on digital subtraction angiograms in the EVT arm using the modified TICI (mTICI) score, and successful reperfusion was defined as mTICI $\geq$ 2b.[21]

Clot Burden Score

Clot extent was determined according to the CBS, which is a 10-point scoring system in which a lower score reflects a more extensive thrombus, as described previously.[8,9] A score of 10 implies clot absence or a clot with no susceptibility vessel sign.[22] A score of 0 implies complete multisegment vessel occlusion. The CBS was subsequently dichotomized using a $\geq$6-point cutoff, according to and for comparison with previous studies.[6,10]

Collateral Score

Collaterals were assessed on baseline FLAIR sequence. FVHs were defined as focal, tubular, or serpentine hyperintensities in subarachnoid spaces with a typical arterial course.[23] Quantification of FVH was performed using an FVH–ASPECTS rating system as described previously.[16,23] An ASPECTS cortical area was considered positive when it coincided with an FVH. The FVH score ranged from 0 (no FVH) to 6 (FVHs abutting all ASPECTS cortical areas). For further analyses, the FVH score was considered in 4 categories (0 versus 1–2 versus 3–4 versus 5–6) to avoid small numbers in extreme FVH scores.

Table 1: Main patient characteristics according to favorable outcome[a]

Characteristics	Favorable Outcome (90-Day mRS 0–2)		P
	No (n = 151)	Yes (n = 165)	
Demographics			
Age (mean) (SD) (yr)	72.8 ± 12.8	64.2 ± 14.1	<.001
Men	77 (51.0)	93 (56.4)	.34
Medical history			
Hypertension	97 (65.1)	77 (47.5)	.002
Diabetes	31 (21.1)	14 (8.5)	.002
Hypercholesterolemia	58 (40.8)	58 (36.0)	.39
Current smoking	16 (12.9)	42 (29.6)	.001
Coronary artery disease	26 (18.2)	18 (11.1)	.08
Current stroke event			
Systolic blood pressure (mean) (SD) (mm Hg)	148 ± 25	144 ± 23	.08
Diastolic blood pressure (mean) (SD) (mm Hg)	82 ± 18	81 ± 14	.50
Glycemia (median) (IQR)	6.8 (5.9–8.4)	6.3 (5.8–7.4)	.01
NIHSS score (median) (IQR)	19 (16–22)	15 (10–19)	<.001
ASPECTS (median) (IQR)	6 (4–8)	7 (6–9)	<.001
Site of occlusion			
M1 MCA	119 (78.8)	144 (87.3)	.10
ICA	28 (18.5)	17 (10.3)	
Tandem	4 (2.6)	4 (2.4)	
Intravenous tPA	72 (47.7)	92 (55.8)	.15
Cardioembolic	57 (38.5)	78 (47.6)	.11
Interval times (median) (IQR) (min)			
Onset-to-groin puncture time	219 (180–266)	216 (170–264)	.33
Onset to imaging	110 (85–145)	112 (85–143)	.89
Onset to clot	254 (200–297)	242 (189–285)	.14

Note:—IQR indicates interquartile range.

[a] Values are (No.) (%) unless otherwise indicated. Onset-to-groin puncture is defined as the interval between the onset of symptoms and the groin puncture; onset to imaging is defined as the interval between the onset of symptoms and the beginning of the first acquisition of MR imaging sequence; and onset to clot is defined as the interval between the onset of symptoms and the first contact of the mechanical thrombectomy device with the clot that occluded the vessel.

Outcome Assessment

Neurologic functional outcome was assessed by the mRS score at 90 days. The mRS ranges from 0 (no residual stroke symptoms) to 6 (death) and was evaluated across the entire score range as an ordinal variable.[24] Favorable outcome was clinical independence, defined as a 90-day mRS score of 0–2. In both trials, the 90-day mRS score was assessed by trained research nurses unaware of the group assignments during face-to-face interviews or via telephone conversations.

Statistical Analysis

Categoric variables were expressed as frequencies and percentages. Quantitative variables were expressed as means (SD) or medians (interquartile range) for non-normal distribution. Normality of distributions was assessed graphically using the Shapiro-Wilk test. Baseline characteristics and outcomes were described in patients included and not included in the primary analysis due to missing CBS values. Between-group imbalances were assessed by calculating absolute standardized differences (Cohen D effect size); an absolute standardized difference >20% was considered meaningful.[25] Comparisons in baseline characteristics according to favorable outcome status (mRS 0–2) were made using the Student t test for Gaussian continuous variables, the Mann-Whitney U test for non-Gaussian continuous variables, and the χ^2 test (or Fisher exact test when the expected cell frequency was <5) for categoric variables, as appropriate. The correlation between the CBS and FVH score was examined by calculating the Spearman rank correlation coefficient.

We assessed the association of favorable outcome with the CBS and FVH score using univariable and multivariable logistic regression models. The shape of relationships was examined by a graphic approach using nonparametric smoothing techniques. Because we observed a non-log-linear relationship between the CBS and favorable outcome, the CBS was also analyzed according to the previously published threshold (≥6).[6,10] The associations were adjusted on study and prespecified confounders (age, sex, admission NIHSS, use of intravenous tPA, and onset-to-groin puncture time). Finally, we explored the interaction between a high CBS (≥6) and the FVH score by including the corresponding multiplicative term in the logistic regression models. To illustrate the interaction, we calculated ORs with their 95% CIs of favorable outcome for a high CBS according to the FVH score (0 versus 1–2 versus 3–4 versus 5–6).

Primary analysis was conducted in patients with available CBS measures. Sensitivity analysis, including all eligible patients, was performed after handling missing values by a multiple-imputation procedure. Missing data were imputed under a missing at random assumption via a regression-switching approach (chained equation with Mean n = 10 imputations) using all baseline characteristics and the study outcome with a predictive mean-matching method for continuous variables and a multinomial or binary logistic regression model for categoric variables.[26] Estimates obtained in the different imputed datasets were combined using the Rubin rules.[27] Statistical testing was conducted at the 2-tailed α-level of .05. Data were analyzed using SAS software, Version 9.4 (SAS Institute).

RESULTS

Of the 793 patients randomized in the ASTER and THRACE trials, 416 patients received thrombectomy following MR imaging–based triage and were eligible for this study (Online Fig 1). Of them, 90 patients without CBS assessment (missing values) were excluded from primary analysis. Main baseline characteristics and outcomes of the study population according to the availability of the CBS are available in Online Table 1. Several meaningful differences were observed (standardized difference, >20%); favorable outcome was observed in 165 of 326 patients with a CBS by comparison with 27 of 90 patients without CBS assessment. Table 1 shows the characteristics of patients in the primary analysis sample, according to favorable outcome (see Online Table 2 for characteristics of all eligible

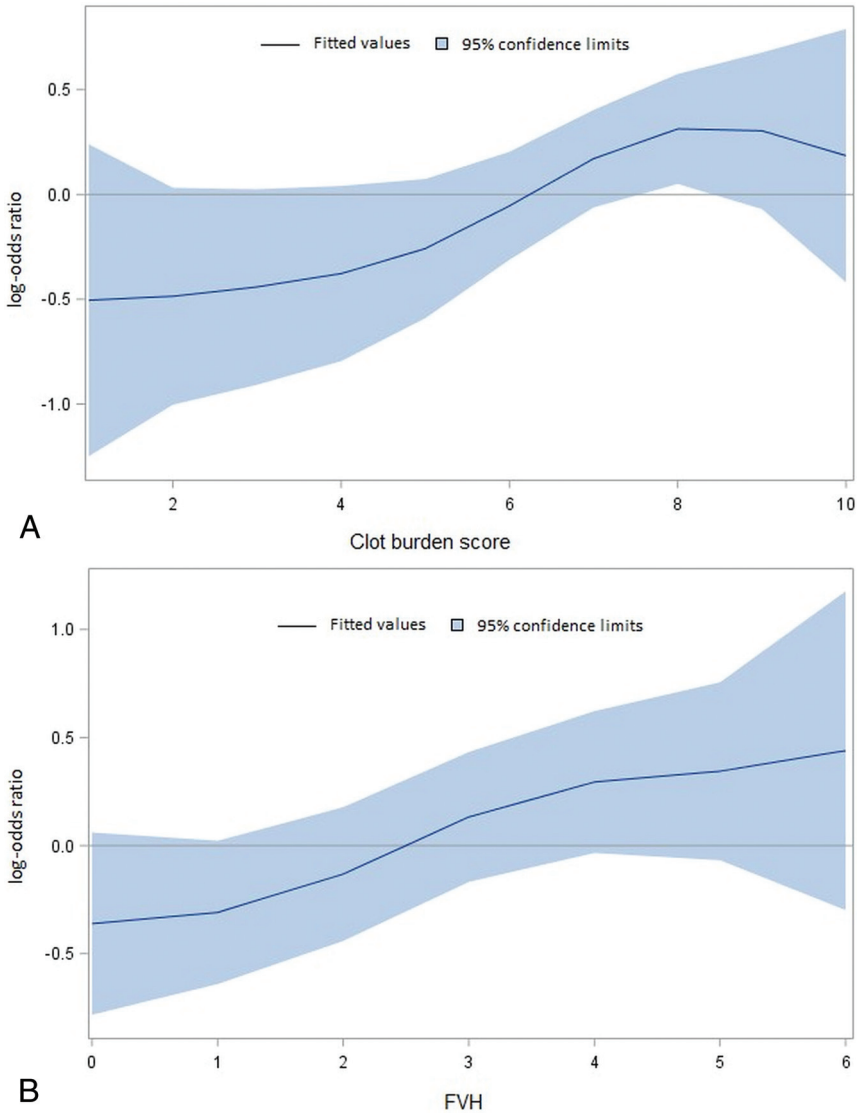

FIG 1. Shape of association of favorable outcome with the CBS (*A*) and FVH score (*B*). Curves were obtained by fitting a generalized additive model (binomial distribution with a logit link function) with a cubic smoothing spline term.

patients after treating missing values by multiple imputation). Patients with favorable outcome were younger and more often smokers, less often had hypertension and diabetes, and had a lower glycemia level at admission, a lower NIHSS score, and a higher ASPECTS than patients without favorable outcome.

Association of Favorable Outcome with the CBS and FVH Score

As shown in Fig 1, the rate of favorable outcome increased with higher CBS (smaller clots) and FVH (higher collaterals) values; for CBS, a non-log-linear relationship was observed. As shown in Table 2, a high CBS (≥6) was significantly associated with an increased likelihood of favorable outcome, with an unadjusted OR of 1.84 (95% CI, 1.13–3.00). Similarly, a significant association was found when the CBS was analyzed as a quantitative trait (unadjusted OR = 1.12; 95% CI, 1.01–1.23 per 1-point increase). After adjustment on prespecified confounders (study, age, sex, admission NIHSS, intravenous tPA, and onset-to-groin puncture time), the association of the CBS and favorable outcome was no longer significant (Table 2). After handling missing values by multiple imputations, every FVH grade increase was significantly associated with an increased likelihood of favorable outcome, with an unadjusted OR = 1.17 (95% CI, 1.03–1.32). In multivariate analysis,

Table 2: Association of favorable outcome with CBS and FVH score

	Favorable Outcome		Unadjusted		Adjusted[b]	
	No	Yes	OR (95% CI)	*P*	OR (95% CI)	*P*
Complete case analysis	(*n* = 151)	(*n* = 165)				
CBS (median) (IQR)	6 (5–8)	7 (6–8)	1.12 (1.01–1.23)[c]	.02	1.05 (0.93–1.19)[c]	.38
≥6 (No.) (%)	95 (62.9)	125 (75.8)	1.84 (1.13–3.00)	.01	1.35 (0.75–2.41)	.31
FVH (median) (IQR)	2 (1–4)	3 (1–4)	1.17 (1.03–1.32)[c]	.01	1.14 (0.98–1.33)[c]	.07
Sensitivity analysis[a]	(*n* = 218)	(*n* = 198)				
CBS (median) (IQR)	6 (4–8)	7 (5–8)	1.15 (1.04–1.26)[c]	.003	1.05 (0.94–1.18)[c]	.37
≥6 (No.) (%)	134 (61.6)	150 (75.6)	1.93 (1.24–3.00)	.003	1.33 (0.78–2.27)	.29
FVH (median) (IQR)	2 (0–3)	3 (1–4)	1.21 (1.08–1.35)[c]	<.001	1.17 (1.02–1.34)[c]	.02

[a] Sensitivity analysis was performed in all patients with MR imaging (*n* = 416) after handling missing values by multiple imputation.
[b] Prespecified adjustment on study (ASTER versus THRACE), age, sex, admission NIHSS, intravenous tPA, and onset-to-groin puncture time.
[c] OR per 1-point increase in CBS or FVH.

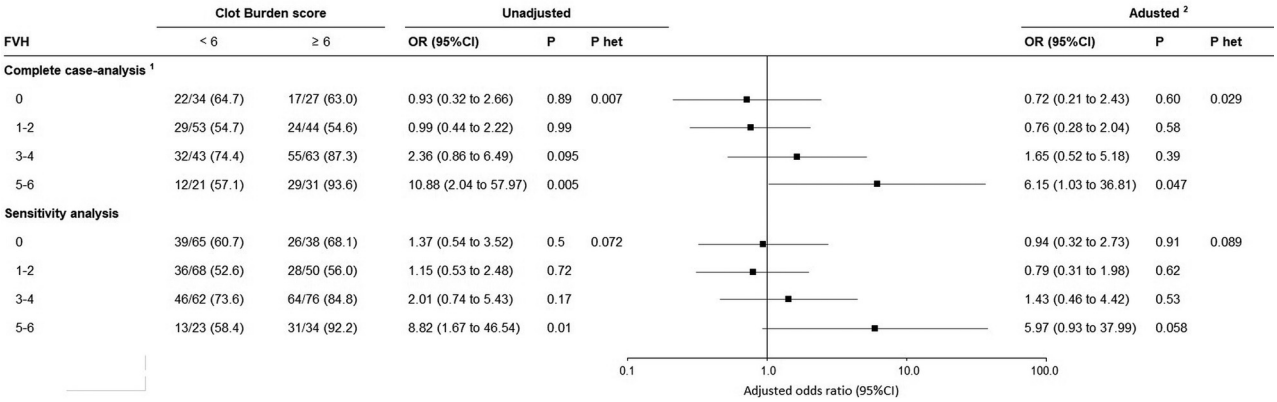

FIG 2. Association of favorable outcome and a high CBS according to the FVH Score. [1]Sensitivity analysis was performed in all patients with MR imaging ($n = 416$) after handling missing values by multiple imputation. [2]Prespecified adjustment on the study (ASTER versus THRACE), age, sex, admission NIHSS, intravenous tPA, and onset-to-groin puncture time. *P* het indicates an interaction test between the clot burden score and the FVH grade (treated as a 6-level ordinal variable).

FVH was of borderline significance in primary analysis (OR = 1.14; 95% CI, 0.98–1.33) and was significant in the sensitivity analysis (OR = 1.17; 95% CI, 1.02–1.34).

The association of successful reperfusion (mTICI ≥ 2b) with the CBS and FVH score is presented in Online Table 3.

Association between the CBS and FVH Score

A weak, positive correlation between the CBS and FVH score was found (Online Fig 2), with a Spearman rank correlation coefficient of 0.20 (95% CI, 0.09–0.31).

Association between a High CBS and Favorable Outcome Modified by the FVH Score

As shown in Fig 2, an interaction was found between a high CBS and FVH grade on favorable outcome, which reached the significance level in primary analysis. The positive association between a high CBS and favorable outcome was mainly observed for the highest FVH grades, with an adjusted OR for the CBS of ≥6 of 6.15 (95% CI, 1.03–36.81) in the primary analysis and 5.97 (95% CI, 0.93–37.99) in sensitivity analysis.

DISCUSSION

In this study, the 3-month functional outcome was better with a higher CBS and a higher FVH score in unadjusted analysis. However, only the FVH score was an independent factor related to outcome in the adjusted analysis. Because an interaction was observed between the CBS and FVH score, we showed an independent stronger association between clot extent (CBS) and functional outcome for patients with good collaterals (FVH ≥5).

A weak positive correlation between the CBS and FVH score was found with a Spearman rank correlation coefficient of 0.20 (95% CI, 0.09–0.31). This observation does not contradict our main results. Furthermore, this is not surprising because the FVH–ASPECTS rating system, unlike the CBS, does not provide a strict ordinal variable.

Thrombus and collaterals can be part of the imaging assessment in patients with AIS and may play a role in clinical practice to guide physicians to the best reperfusion strategy.[28] Recently, Seners et al[29] showed that better collaterals, smaller thrombus, and more distal occlusion sites were independently associated with early post-IVT recanalization in patients eligible for EVT. Thus, advanced imaging may play a key role in personalized medicine in identifying which patients with large-vessel occlusion are most likely to benefit from reperfusion therapies.

Associations of thrombus location and the length of the occlusion with functional outcome and recanalization are well-described in patients treated with IVT,[30] and recently in patients undergoing EVT.[6,10] Both parameters are included in the CBS, in which a lower score reflects a more extensive thrombus.[8,9] Patients with a lower CBS (longer thrombus) have lower odds of reperfusion, larger final infarct volumes at follow-up, and worse functional outcome.[7,10] Besides, longer thrombi may be more difficult to retrieve, requiring more attempts and prolonging the procedural time.[7,31]

Few studies have assessed the relation between collateral status and clot extent and the role of collateral status in the association of clot extent with functional outcome.[13,14] Our findings are in accordance with previous studies in which patients with poor baseline collaterals had longer clots.[13,32] Patients with proximal occlusion in the anterior circulation (ICA and proximal M1) are likely to have a greater amount of brain tissue at risk because of the involvement of the lenticulostriate vessels and poorer collateral status because of decreased collateral flow via the anterior cerebral artery pial vessels.[7] Conversely, patients with a smaller clot are more likely to have patent anterior cerebral arteries and posterior communicating arteries, leading to increased pial collateral flow.[14] Moreover, collateral status and arterial branching patterns may influence clot length and clot characteristics.[13] Qazi et al[13] suggested that patients with poor collaterals and/or inefficient angioarchitecture—defined as the absence of branching arteries around the original clot despite collaterals that lead to the secondary thrombus extension—will have longer clots extending into the pial arteries because of blood flow stagnation.

Our study, with a larger population sample size screened with first-line MR imaging and treated by EVT for AIS, confirms a previous one in which a significant effect of collateral status on the association of clot extent and clinical outcome was observed in patients with moderate and high collateral scores, supporting

the thesis that collateral circulation at least partially underlies the association between clot extent and functional outcome.[14]

Indeed, the optimal imaging technique for efficient patient triage in the acute setting remains a conundrum. CT offers the advantages of being fast, almost universally available, and conspicuous for hemorrhage. However, CTA may overestimate the extent of thrombus involvement. Indeed, if the collateral circulation is weak or with short delays between contrast injection and imaging acquisition,[33] an overestimation of clot length is possible. Furthermore, the current methods of collateral assessment with CTA require expert image evaluation and, though shown to be applicable in clinical trials, can be prone to measurement error in less expert hands.[34] Of note, CT perfusion, which also provides accurate collateral assessment, could overcome issues of CTA timing with the temporal maximum intensity projection of CT perfusion, which gives a relevant reflection of the CBS.[35,36]

Although less readily available, MR imaging is more sensitive for ischemic extent, the presence of hemorrhage, thrombus characterization, and stroke mimics and can be used as a prime and sole imaging technique without delaying treatment decisions.[37] FLAIR and T2* sequences have several advantages over traditional imaging techniques for detecting collaterals and thrombus; this technique is routinely used in all MR imaging units, requires a relatively short scan time, and requires no exogenous contrast agent or radiation exposure. Furthermore, T2*-CBS and the FVH score reproducibility have been demonstrated in multiple studies,[9,10,16,18] and images are assessable by the naked eye directly on any DICOM viewer without the need for postprocessing. Nevertheless, in our study, we did not use the thrombus size but rather the T2*-CBS, which is, by definition, an overestimation of the clot length through the extent of the blooming effect.

Strengths and Limitations

The strengths of this study include the analysis of the CBS and FVH score in 2 randomized, multicenter study designs that evaluated highly effective thrombectomy devices and that included patients irrespective of clot length and collateral status. To our knowledge, this is also the first study to assess the interaction effect of collateral status assessed by the FVH score on functional outcome based on clot extent in patients with AIS. Taken together, our data provide insight into the association between clot extent and functional outcome, which appears to be partially explained by a higher collateral score leading to a smaller clot.

However, our study also has limitations. First, patients were included on the basis of the criteria of the 2 randomized controlled trials, leading to a selection bias. Second, in the emergency setting for AIS, the acquisition of MR imaging may be impossible in patients who are claustrophobic or in patients who cannot be still, especially with dominant-hemisphere strokes. Third, FVH collateral grading can quantify the abundance of the vasculature, but not the flow velocity, and this feature may be relevant in acute stroke triage: Plentiful collaterals with fast delivery may designate a patient who will benefit more from EVT than a patient with plentiful-but-slow collaterals with late delivery.[38] Fourth, the CBS quantifies thrombi but omits information on characteristics that are relevant for outcome, (ie, perforators occlusion). Indeed, as emphasized by Qazi et al,[13] the thrombus extent can have different implications through the angioarchitecture patterns. However, we were unable to assess the anterior temporal artery and perforator artery patency in our study. Fifth, there was no imaging or histologic characterization of clot nature to further characterize the relationship of EVT results with clot types. Indeed, a CBS of 10 implies clot absence or a clot with no susceptibility vessel sign, the latter situation representing between 20% and 30% of occlusions.[39] Additionally, MR imaging acquisition parameters of the gradient recalled-echo sequence were left to the discretion of the recruitment centers; and the susceptibility vessel sign, used to quantify the CBS, is known to be a radiologic marker that varies among MR imaging scanners.[40] However, this lack of standardization, which, in fact, corresponds to the real-life daily use of MR imaging sequences, points out the generalizability of our findings. Indeed, previous similar pragmatic multicentric assessments of the CBS have already emphasized clinically relevant results.[10] Finally, we did not assess the predictive power of patient selection. Future studies should evaluate the clinical utility of such radiomarkers in the screening of candidates for endovascular treatment in case of large-vessel occlusion and to elucidate the pathways linking collateral status to clot extent and vice versa.

CONCLUSIONS

There is an influence of collateral status, quantified by the FVH scoring system, on the association of clot extent with functional outcome. The independent association of a high FVH score and good functional outcome at 3 months supports the idea that the FVH score might be a prognostic factor, especially when contrast-based vascular imaging is not available. Future work should assess the mechanism underlying the interaction between thrombus extent and collaterals.

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