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ABSTRACT

BACKGROUND AND PURPOSE: Pretreatment CTA-based Cortical Vein Opacification Score (COVES) has been shown to predict good functional outcomes at 90 days in patients with acute ischemic stroke secondary to large vessel occlusion (AIS-LVO). This is thought to be related to its ability to measure collateral status (CS). However, its association with the reference standard test, the DSA-based American Society of Interventional and Therapeutic Neuroradiology (ASITN) collateral score, has yet to be established. Therefore, this study assesses the relationship between COVES and ASITN CS.

MATERIALS AND METHODS: In this prospectively collected, retrospectively reviewed analysis, patients with anterior circulation LVO from September 1, 2017, to October 1, 2023, were included. The COVES grading, which ranges from 0 to 6, was independently assessed by 2 board-certified neuroradiologists. The ASITN CS was independently assessed by a board-certified neuroradiologist and the performing neurointerventionalist. Any discrepancies were resolved through consensus review. Spearman rank correlation, univariable logistic regression, multivariable logistic regression, and receiver operating characteristic curve analysis were performed. A P value of $\leq .05$ was considered significant.

RESULTS: In total, 311 consecutive patients (median, IQR = 68 years [59–78 years]; 55.9% women) met our inclusion criteria. There was significant positive correlation between COVES and ASITN CS ($\rho = 0.41$, $P < .001$), and higher COVES was significantly and independently associated with good ASITN CS (unadjusted-OR = 1.74, $P < .001$) and adjusted-OR = 1.73, $P < .001$). Receiver operating characteristic curve analysis showed area under the curve of 0.71, $P < .001$).

CONCLUSIONS: By demonstrating the independent association of COVES with the reference standard test for collateral status assessment, the ASITN CS, we further validate the role of COVES in estimating collateral status.

ABBREVIATIONS: AIS = acute ischemic stroke; aOR = adjusted odds ratio; ASITN = American Society of Interventional and Therapeutic Neuroradiology; AUC = area under the curve; CS = collateral status; COVES = Cortical Vein Opacification Score; ECASS = European-Australasian Acute Stroke Study; HIR = hypoperfusion intensity ratio; IVT = intravenous thrombolysis; LVO = large vessel occlusion; mCTA = multiphase CTA; MT = mechanical thrombectomy; OR = odds ratio; PH = parenchymal hematoma; rCBF = relative cerebral blood flow; ROC = receiver operating characteristic curve; Tmax = time to maximum; uaOR = unadjusted odds ratio; VO = venous outflow

Robust collateral status (CS) is associated with better reperfusion and subsequent better functional outcomes in patients with anterior circulation acute ischemic stroke caused by large vessel occlusion (AIS-LVO).[1-7] The DSA-derived 5-point American Society of Interventional and Therapeutic Neuroradiology (ASITN) scale is considered the reference standard test in quantifying CS.[8] ASITN CS is an excellent marker in predicting the outcomes in AIS-LVO following mechanical thrombectomy (MT). However, DSA CS can only be assessed intraoperatively, preventing preplanning of the intervention. This makes it critical to have reliable pretreatment surrogate CS markers.[9-14]

Arterial collaterals from interconnected pial arteries overlying the brain surface may temporarily preserve blood flow to otherwise critically hypoperfused brain tissue.[15-17] Arterial collateral

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SUMMARY

PREVIOUS LITERATURE: COVES quantifies contrast opacification of superficial and deep venous structures on the affected side, serving as a surrogate marker for collateral status in the affected hemisphere of patients with acute ischemic stroke due to large vessel occlusion.

KEY FINDINGS: COVES is independently associated with the reference standard test for assessing collateral status, the DSA-derived ASITN scale.

KNOWLEDGE ADVANCEMENT: While the association between COVES and ASITN scales had not been previously established, this study demonstrates a significant relationship between COVES and the ASITN collateral score. This further validates the role of COVES in estimating collateral status.

assessment, however, is only 1 factor of CS. Comprehensive CS assessment includes arterial blood flow through the brain tissue and into draining veins.[18] Furthermore, robust venous outflow (VO) is strongly correlated with robust pial arterial collaterals and excellent tissue perfusion.[18-24]

Hence, poor VO may result from poor pial arterial collateral flow and hampered blood transit through the tissue itself. Therefore, the presence of contrast in venous structures in the affected hemisphere on CTA serves as a measure of VO and quantifies tissue perfusion.[15-17] Single-phase CTA-based Cortical Vein Opacification Score (COVES)[15] is 1 such parameter that quantifies contrast opacification of superficial and deep venous structures on the affected side and has been shown to be a strong surrogate marker for tissue perfusion[25]

In this study, we aimed to investigate the relationship between COVES as pretreatment single-phase CTA marker of CS with the reference standard DSA ASITN CS based on ASITN criteria. We hypothesize that higher COVES is associated with more robust CS on DSA. Additionally, the relationship between COVES and the CTA-based Tan score, multiphase CTA CS, CTP-based CS, the hypoperfusion intensity ratio (HIR), and other CTP-based measures, such as relative cerebral blood flow (rCBF) $< 30\%$, time to maximum (Tmax) > 6 seconds, and mismatch volume, was also studied.

MATERIALS AND METHODS

Study Design

A retrospective analysis of prospectively maintained stroke databases was performed, and we identified consecutive patients from 2 comprehensive stroke centers from September 01, 2017, to October 01, 2023, who met our inclusion criteria. This study was approved through the Johns Hopkins Institutional Review Board (IRB00269637) and follows the STROBE checklist guidelines as an observational study[26] (Supplemental Data).

Study Participants

The inclusion criteria for this study were: 1) MT triage within 24 hours of symptom onset or last known well; 2) diagnostically adequate multimodal pretreatment CT imaging including NCCT and CTA; 3) AIS due to a CTA-confirmed large vessel occlusion of proximal supraclinoid ICA, ICA terminus, MCA occlusion, specifically including M1 and proximal M2 segments of the MCA[27]; 4) those who had recorded ASITN CS.[8]

The study was conducted in accordance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act (HIPAA). Informed consent was waived by the institutional review boards, given the retrospective study design. The decisions to administer IV thrombolysis (IVT) and/or perform MT were made on an individual basis based on consensus stroke team evaluation per institutional protocols.

CTP Image Acquisition

CT perfusion data were obtained by using a Somatom Force (Siemens) scanner. The acquisition parameters included 70 kVp, 200 effective mAs, a rotation time of 0.25 seconds, an average acquisition time of 60 seconds, collimation of 48×1.2 mm, a pitch value of 0.7, and a 4D range of 114 mm $\times$ 1.5 seconds.

Data Collection

Baseline and clinical data were collected through electronic records and stroke center databases for each patient, including but not limited to demographics, site of occlusion, TOAST classification,[28] baseline CT parameters at first presentation, and outcome measures. The presence of hemorrhage was also reported on subsequent CT/MR based on the European-Australasian Acute Stroke Study (ECASS[29]) classification during the same admission. Symptomatic hemorrhage was defined as ECASS parenchymal hematoma (PH) 1 or PH2.

Imaging Analysis

All the CTAs were assessed by board-certified neuroradiologists (9 years of working experience) for diagnostic adequacy and timing of contrast bolus, where only those deemed diagnostic adequate as defined by evidence of contrast opacification of 1 of the sigmoid sinus jugular bulbs[15] were included in the study.

The COVES grading[16] was independently assessed by board-certified neuroradiologists (1 with 9 years of working experience and another with 5 years). COVES scores ranged from 0 to 6. COVES score of 0–2 is considered poor collateral filling, and COVES score of 3 to 6 is considered good collateral filling.

This score was obtained by assessing venous opacification as absent (0), partial (1), or full (2) for the vein of Labbé, sphenoparietal sinus, and superficial middle cerebral vein for the cerebral hemisphere ipsilateral to the occlusion.[15]

The DSA CS was independently assessed by a board-certified neuroradiologist (9 years of working experience) and the performing

Table 1: Spearman rank correlation analysis of COVES (per point) with DSA, CTP, and CTA-based collateral score markers

Correlation Analysis of COVES and following Imaging and Outcome Measures	Spearman Rho	95% CI		*P* Value
DSA collateral score marker				
ASITN collateral score	0.409	0.312	0.497	.000
CT perfusion markers				
rCBF <30% (in mL)	−0.300	−0.395	−0.199	.000
Tmax >6 seconds (in mL)	−0.430	−0.514	−0.339	.000
Mismatch volume (in mL)	−0.359	−0.449	−0.262	.000
HIR	−0.350	−0.441	−0.252	.000
CTA collateral score marker				
Tan score	0.506	0.433	0.573	.000
Multiphase CTA collateral score	0.536	0.455	0.608	.000

neurointerventionalist. Any discrepancies were resolved based on consensus review. ASITN grades included grade 0: nonexisting or barely visible pial collaterals on the ischemic site during any point of time; grade 1, partial collateralization of the ischemic site until the late venous phase; grade 2, partial collateralization of the ischemic site by the late venous phase; grade 3, complete collateralization of the ischemic site by the late venous phase; and grade 4, complete collateralization of the ischemic site before the venous phase.[8]

Commercial RapidAI perfusion software, Version 5.2.2 (iSchemaView), was used to generate quantitative perfusion parameters, including rCBF <30% Tmax >6 seconds, and mismatch volumes. Additionally, the software automatically provided the HIR, which is the ratio of Tmax >10 seconds volume to Tmax >6 seconds volume.[30] Mismatch volume was defined as the difference between the volume of Tmax >6 seconds and the volume of rCBF <30%.[31] Please do note that quality assessments of the CT perfusion data were performed independently of the outcomes by a board-certified neuroradiologist with 9 years of experience.

The Tan score was calculated by using a 4-point grading system, ranging from 0 to 3, to evaluate arterial filling in the affected territory, where a score of 1 indicates arterial contrast filling of ≤50% of the occluded MCA territory, a score of 2 indicates filling in >50% but <100%, and a score of 3 indicates filling in 100% of the occluded territory.[32]

The multiphase CTA (mCTA) collateral score was calculated by using a 6-point grading system, ranging from 0 to 5.[33] The score of 5 indicates no filling delay compared with the asymptomatic contralateral hemisphere and normal pial vessels in the affected hemisphere; 4 indicates a filling delay of 1 phase with unchanged extent and prominence of pial vessels; 3 indicates a filling delay of 2 phases or a 1-phase delay with a significantly reduced number of vessels in the ischemic territory; 2 indicates a 2-phase delay with a significantly reduced number of vessels or a 1-phase delay showing regions without visible vessels; 1 indicates only a few vessels visible in the affected hemisphere during any phase; and 0 indicates no vessels visible in the affected hemisphere during any phase.

Statistical Analysis

Descriptive statistics were employed to summarize patient data. Categoric data were presented by using contingency tables, which included counts and percentages, while continuous variables were summarized with median values and interquartile ranges. For data analysis, a Student *t* test was used for continuous variables, the Mann-Whitney *U* test was applied to ordinal data, and the χ^2 test was utilized for categoric data. Interrater reliability was measured by using Cohen κ coefficient (k). Spearman rank correlation analysis assessed the correlation between 2 variables.

Additionally, both univariable and multivariable logistic regression analyses were conducted to estimate the unadjusted odds ratio (uaOR) and adjusted odds ratio (aOR) for the dichotomized outcome measures of ASITN CS and HIR. Receiver operating characteristic curve (ROC) analysis was performed to determine the area under the curve (AUC) for these measures. The ASITN and HIR scores were dichotomized as follows: the ASITN CS score was categorized as "good" (scores of 3 or 4) and "bad" (scores of 0 to 2) collateral status, based on existing literature.[34] Similarly, an HIR score of less than 0.4 was classified as a "good" tissue-level collateral score, while a score of more than 0.4 was classified as a "poor" tissue-level collateral score, also in accordance with established literature.[21,35-41] A *P* value of ≤.05 was considered statistically significant.

RESULTS

A total of 311 consecutive patients, median age of study population 68 years (IQR: 59–78 years) and 174 (55.9%) women, met our inclusion criteria. In total, 113 (36.3%) patients received IVT.

Of 311 patients, 226 (72.7%) had M1 segment occlusion, 60 (19.3%) had proximal M2 segment occlusion, and 25 (8.04%) had supraclinoid ICA segment occlusion. Patient demographic and stroke treatment details are presented in Supplemental Data.

Distribution of COVES scores in patients with good and poor CS defined by ASITN CS is illustrated in Supplemental Data.

Relationship between COVES and DSA CS

A positive correlation was observed between COVES and ASITN CS ($\rho = 0.41$, 95% CI: 0.31–0.50, $P < .001$) (Table 1). Higher COVES scores (per point) were associated with good ASITN CS, defined as a DSA ASITN score of 3 or 4, with an uaOR of 1.74 (95% CI: 1.47–2.01, $P < .001$) (Table 2). ROC analysis revealed an AUC of 0.71 (95% CI: 0.65–0.77) for predicting good DSA CS (Table 2).

Multivariable logistic regression analysis, accounting for multiple confounding variables including age (per 10 years), sex, hypertension, hyperlipidemia, diabetes, heart disease, atrial fibrillation, prior transient ischemic attack or stroke, intravenous thrombolysis administration, admission NIH Stroke Scale, and premorbid mRS, showed an independent association of COVES with good DSA CS (aOR of 1.73, 95% CI: 1.44–2.09, $P < .001$) (Table 3).

Table 2: ROC curve and univariable logistic regression analysis of COVES with other DSA and CTP collateral score markers and with functional outcome measures

Outcome Measures	ROC Analysis				Logistic Regression Analysis			
	AUC	95% CI		*P* Value	uaOR	95% CI		*P* Value
DSA American Society of Interventional and Therapeutic Neuroradiology Collateral score (3–4)	0.708	0.648	0.767	.000	1.741	1.470	2.062	.000
Hypoperfusion intensity ratio (< 0.4)	0.685	0.629	0.742	.000	1.603	1.366	1.881	.000
90-day mRS of 0–2	0.560	0.503	0.617	.038	1.150	1.013	1.304	.030
Symptomatic hemorrhagic transformation	0.635	0.550	0.720	.002	0.726	0.585	0.901	.004

Table 3: Univariable and multivariable logistic regression model in predicting good collateral status as defined by DSA ASITN collateral score of 3 or greater

	uaOR	95% CI		*P* Value	aOR	95% CI		*P* Value
COVES score (per point)	1.741	1.470	2.062	.000	1.731	1.436	2.087	.000
Age (per 10 years)	0.957	0.836	1.096	.527	1.005	0.833	1.211	.962
Sex (female)	0.689	0.443	1.074	.100	0.683	0.401	1.161	.159
Hypertension	0.699	0.419	1.163	.168	0.636	0.335	1.205	.165
Hyperlipidemia	1.069	0.691	1.655	.764	1.045	0.611	1.786	.872
Diabetes	1.103	0.675	1.802	.697	1.105	0.592	2.061	.754
Heart disease	0.909	0.588	1.406	.669	1.118	0.620	2.014	.711
Atrial fibrillation	0.924	0.590	1.449	.731	0.722	0.385	1.351	.308
Prior stroke/transient ischemic attack	0.960	0.556	1.657	.884	1.019	0.523	1.982	.957
Intravenous thrombolysis	1.241	0.790	1.950	.348	1.377	0.809	2.343	.238
Admission National Institutes of Health Stroke Scale (per point)	0.949	0.920	0.979	.001	0.963	0.928	1.000	.049
Premorbid mRS (per point)	1.116	0.913	1.365	.285	1.031	0.796	1.335	.819

Table 4: Univariable and multivariable logistic regression model in predicting good tissue level collateral status as defined by HIR less than 0.4

	uaOR	95% CI		*P* Value	aOR	95% CI		*P* Value
COVES score (per point)	1.603	1.366	1.881	.000	1.466	1.231	1.747	.000
Age (per 10 years)	1.012	0.883	1.160	.860	0.913	0.759	1.099	.336
Sex (female)	0.646	0.419	0.996	.048	0.589	0.352	0.983	.043
Hypertension	1.428	0.843	2.418	.185	1.805	0.934	3.488	.079
Hyperlipidemia	1.477	0.961	2.271	.075	1.202	0.715	2.022	.488
Diabetes	1.352	0.846	2.163	.208	1.333	0.751	2.366	.326
Heart disease	1.352	0.846	2.163	.208	0.506	0.282	0.909	.023
Atrial fibrillation	0.661	0.431	1.012	.057	1.222	0.663	2.252	.520
Prior stroke/transient ischemic attack	0.999	0.644	1.547	.995	0.937	0.497	1.767	.842
Intravenous thrombolysis	0.656	0.413	1.044	.075	0.619	0.360	1.064	.083
Admission National Institutes of Health Stroke Scale (per point)	0.914	0.885	0.943	.000	0.917	0.883	0.952	.000
Premorbid mRS (per point)	1.178	0.986	1.407	.072	1.250	1.000	1.562	.050

Relationship between COVES and CT Perfusion-Based Collateral Markers

The CT perfusion-based tissue-level collateral score marker, HIR, showed a negative correlation with COVES ($\rho = -0.35$, $P < .001$). Logistic regression analysis, by using HIR less than 0.4 as a marker for good tissue-level collateral status, indicated an uaOR of 1.60 (95% CI: 1.37–1.88, $P < .001$). ROC analysis demonstrated an AUC of 0.69 (95% CI: 0.63–0.74, $P < .001$) (Table 2).

Multivariable logistic regression analysis, controlling for the same confounding variables, revealed an independent association of COVES with good HIR (aOR of 1.46, 95% CI: 1.23–1.74, $P < .001$) (Table 4).

Relationship between COVES and Other CTA Collateral Markers

A positive correlation was observed between COVES and various CTA collateral score markers. COVES showed a positive correlation with the CTA-based Tan score ($\rho = 0.51$, $P < .001$) and the multiphase CTA collateral score ($\rho = 0.54$, $P < .001$) (Table 2).

Relationship between COVES and Other CT Perfusion Parameters

A negative correlation was found between COVES and quantitative CT perfusion parameters that quantify ischemic and infarct volumes. Higher COVES scores correlated with lower rCBF < 30% volume ($\rho = -0.30$, $P < .001$), lower Tmax >6 seconds volume ($\rho = -0.43$, $P < .001$), and lower mismatch volume ($\rho = -0.36$, $P < .001$) (Table 2).

Relationship between COVES and Functional Outcomes

Higher COVES scores were associated with better functional outcomes at 90 days (defined as a 90-day mRS of 0–2), with an uaOR of 1.15 ($P < .05$). Furthermore, higher COVES scores were associated with lower odds of symptomatic hemorrhagic

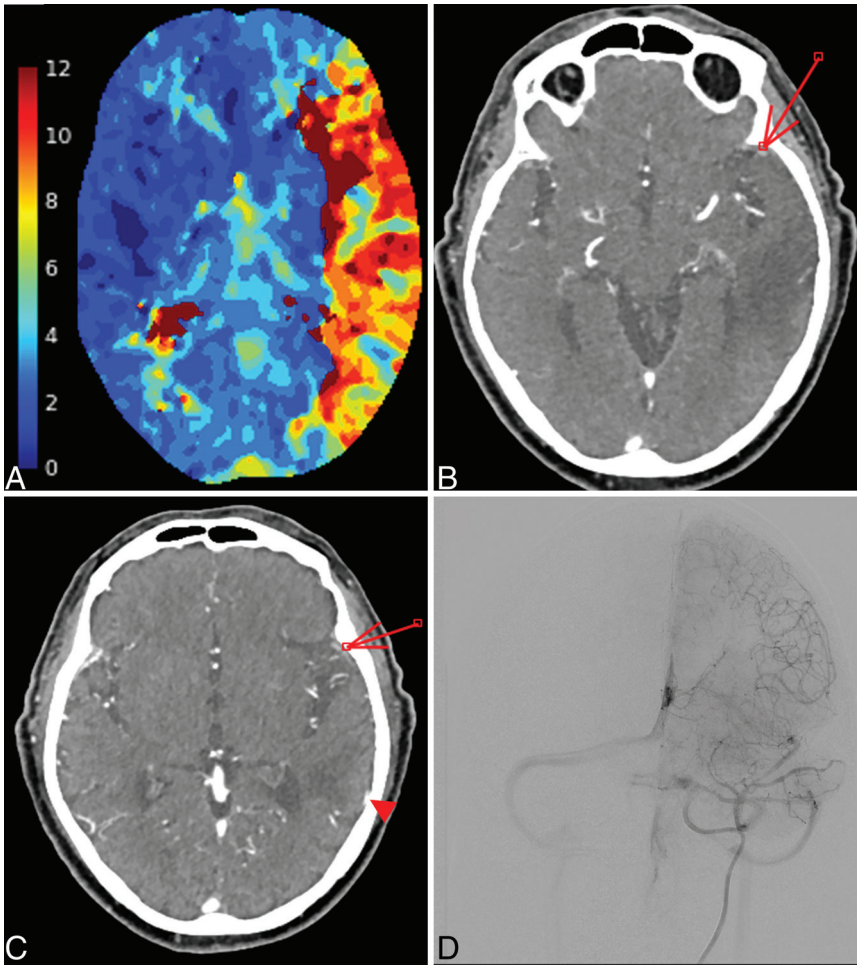

FIG 1. Images from a 75-year-old man who presented with a left M1 occlusion acute ischemic stroke. The RapidAI-derived Tmax perfusion map (*A*), axial CTA at different levels (*B-C*), and preintervention DSA image in the anterior-posterior view during the late venous phase (*D*) are shown. There is delayed contrast transit in the left MCA territory on the Tmax perfusion map (*A*). Images from the affected hemisphere (*B-C*) demonstrate full opacification of the sphenoparietal sinus (*B, arrow*), superficial middle cerebral vein (*C, arrow*), and vein of Labbé (*C, arrowhead*). This resulted in a COVES score of 6. The preinterventional DSA shows intermediate to good leptomeningeal retrograde filling (ASITN grade 3).

transformation (ECASS PH1 or PH2), with an uaOR of 0.73 ($P < .001$). ROC analysis indicated an AUC of 0.56 ($P < .05$) for predicting good 90-day functional outcomes and an AUC of 0.64 ($P < .01$) for predicting symptomatic hemorrhagic transformation (Table 2).

Interobserver Analysis

The interrater reliability for the COVES score on baseline CTA source images was substantial ($\kappa = 0.77$), and the reliability for the ASITN score on the first angiogram was also substantial ($\kappa = 0.70$).

DISCUSSION

Our study demonstrates that COVES is independently associated with the reference standard DSA ASITN CS. This is the first study to explore the associations between COVES, as a baseline CTA CS parameter, and DSA ASITN CS. Furthermore, COVES is independently associated with the CTP-based tissue-level CS marker, the HIR. Additionally, COVES showed a strong correlation with the CTA-based Tan score, mCTA collateral score, and other perfusion parameters.

Tissue perfusion is determined by arterial input and VO; hence, arterial collateral assessment alone may not capture the entire tissue perfusion. VO, on the other hand, depends on arterial input and venous drainage.[15-17] Hence, poor VO may result from poor pial arterial collateral flow and hampered blood transit through the tissue itself. The quantification of VO theoretically better quantifies the tissue perfusion compared with markers of arterial collateral assessment.[15-17]

Single-phase CTA-based COVES,[15] which quantifies the venous outflow, has shown to be associated with MT success[15,42] and better functional outcomes following MT.[1,25,42-44] Hoffman et al[43] showed a correlation of COVES with functional outcomes as defined by 90-day mRS following MT in AIS-LVO. Furthermore, Winkelmeier et al[44] reported that COVES was associated with 90-day mRS independent of recanalization success, premorbid mRS, and NIHSS in patients with extensive baseline infarcts (ASPECTS ≤5) following MT.[44] Moreover, Jansen et al[15] report that absence of cortical vein opacification (COVES = 0) had no benefits following MT. Xia et al[45] report that COVES = 0 is associated with early brain edema and a higher risk of malignant cerebral edema. More recently, Faizy et al[42] conducted a large multicenter study involving 565 patients with anterior circulation AIS-LVO, reporting that favorable COVES was associated with MT success and good 90-day mRS outcomes. Therefore, our novel study aims to explore the direct association of COVES with DSA collateral status, further contributing to the growing evidence for COVES as a CTA-based collateral status marker.

Additionally, HIR derived from quantitative perfusion imaging provides a nuanced measure of tissue-level collateral blood flow and microvascular perfusion in patients with AIS-LVO. Previous studies have linked HIR to collateral circulation, cerebral infarct growth, and clinical outcomes after mechanical thrombectomy. HIR is recognized as a robust and reliable indicator of microvascular collateral flow in stroke. However, the post-processing steps required to generate quantitative perfusion maps demand higher computational resources, which may not be readily available at all institutions, particularly smaller centers. COVES, by its independent association with HIR, can enhance the value of CTA imaging and serve as a potential marker for

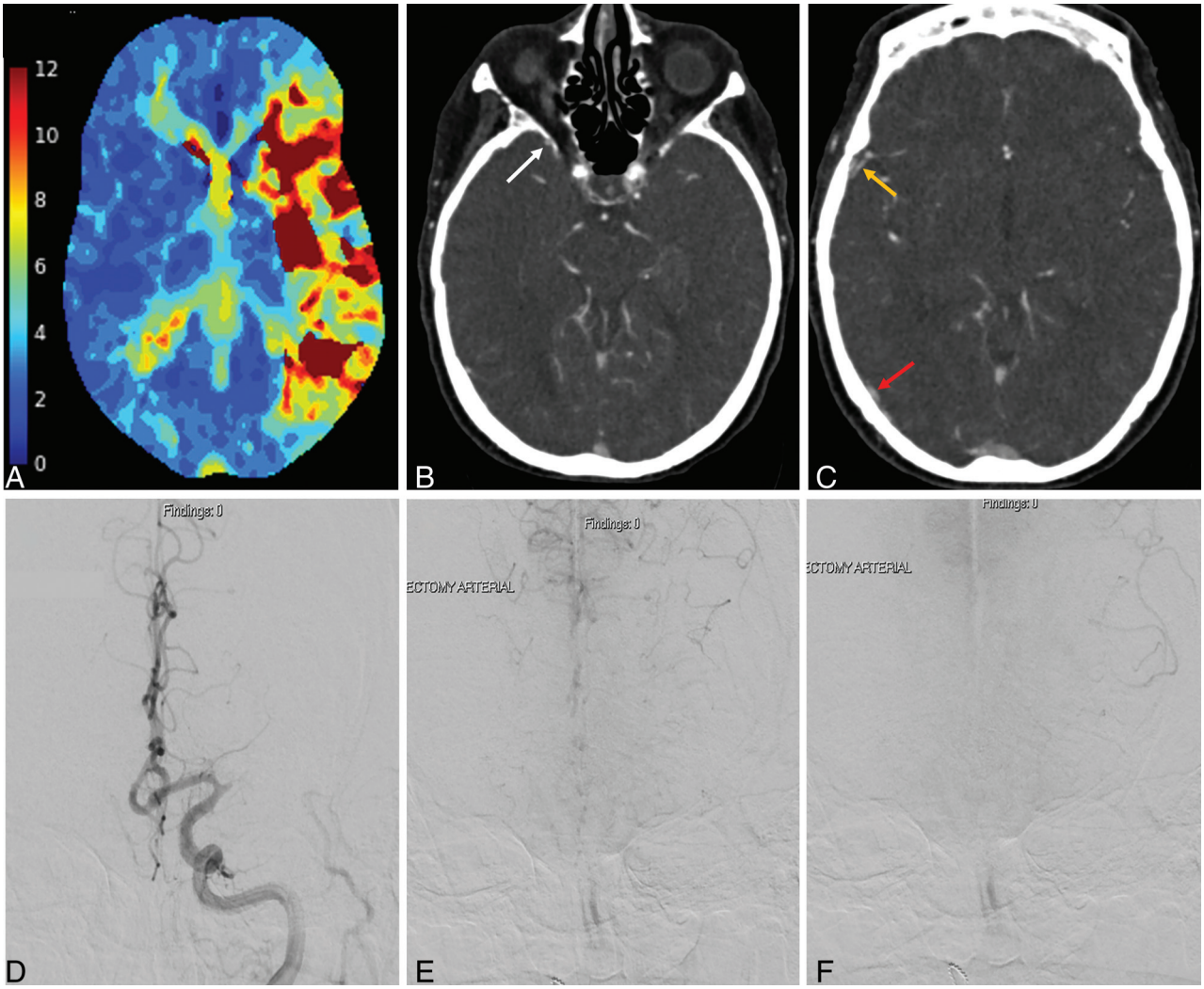

FIG 2. Images from a 74-year-old man who presented with a left M1 occlusion acute ischemic stroke. The RapidAI-derived Tmax perfusion map (*A*), axial CTA at different levels (*B-C*), and preintervention DSA images in the anterior-posterior view during the early arterial phase (*D*), parenchymal (*E*) and later venous (*F*) phases are shown. There is delayed contrast transit in the left MCA territory on the Tmax perfusion map (*A*). Images from the contralateral unaffected hemisphere (*B-C*) demonstrate opacification of the sphenoparietal sinus (*B, white arrow*), superficial middle cerebral vein (*C, yellow arrow*), and vein of Labbé (*C, red arrow*). Whereas, on the affected hemisphere there is no opacification of sphenoparietal sinus (*B*), superficial middle cerebral vein (*C*), and vein of Labbé (*C*), resulting in a COVES score of 0. The preinterventional DSA shows poor leptomeningeal retrograde filling of the initial antegrade capillary blush deficit (target downstream territory; ASITN grade 1).

collateral status.[37] Furthermore, a recent Efficacy and Safety of Thrombectomy in Stroke With Extended Lesion and Extended Time Window (TENSION) trial[46] showed that patient selection based on noncontrast CT alone predicted better functional outcome and lower mortality in AIS-LVO following MT. Hence, having CTA-based CS assessment tools would be of benefit to AIS-LVO cases.

A significant correlation between COVES and mCTA, as well as the Tan score, was observed, as expected. Higher COVES was associated with lower odds of symptomatic hemorrhage and better functional outcomes at 90 days. Additionally, elevated COVES correlated with reduced volumes of rCBF $<$30%, Tmax $>$6 seconds, and mismatch volume. These observations are consistent with findings reported in the literature (Fig 1 and 2).

There are limitations to this study to acknowledge. First, limitations are inherent to retrospective analysis. Second, DSA CS has a modest inter- and intraobserver agreement of DSA CS.[47] Our study is, however, strengthened by our sample size of 311 derived from our prospectively maintained databases from 2 comprehensive stroke centers.

CONCLUSIONS

By demonstrating the independent association of COVES with the reference standard test for collateral status assessment, the ASITN CS, we further validate the role of COVES in estimating collateral status. Future studies are needed to enhance our understanding of the adjunct role of COVES alongside other similar pretreatment imaging-based markers in clinical evaluation and decision-making for patients with acute ischemic stroke and large vessel occlusion.

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