Cortical Vein Opacification for Risk Stratification in Anterior Circulation Endovascular Thrombectomy

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Introduction: There is continued interest in identifying factors that predict a favorable outcome after endovascular thrombectomy (EVT) for anterior circulation large vessel occlusion (ACLVO). We compared the predictive values of 2 different scoring systems for evaluating venous collateral circulation. *Methods:* A retrospective review of patients who underwent EVT for ACLVO at a single institution was performed. Those who underwent preprocedural computed tomography angiography (CTA) were selected. The Cortical Vein Opacification Score (COVES) and Prognostic Evaluation based on Cortical vein score difference In Stroke (PRECISE) score were calculated from each patient's CTA. Our primary outcome of interest was the Modified Rankin Scale (mRS) score at 90 days. *Results:* A total of 103 patients were included in the study (average age = 68.3 years, median National Institutes of Health Stroke Scale = 15). The mean time to reperfusion was 6.4 hours and Thrombolysis in Cerebral Infarction 2B or 3 reperfusion was achieved in 77.7% of cases. An unfavorable COVES score was significantly associated with an unfavorable (mRS 3-6) outcome (adjusted odds ratio [aOR]: 3.06; 95% confidence interval [CI] 1.15-8.13, *P* = .025), while an unfavorable PRECISE score was not (aOR: 1.02; 95% CI .37-2.80, *P* = .966). Based on the Receiver Operating Characteristic analysis, the COVES score had a sensitivity of 68.1%, specificity of 71.4%, and area under the curve (AUC) of .77. The PRECISE score had a sensitivity of 68.9%, specificity of 70.7%, and the AUC of .73. *Conclusions:* The COVES score, but not the PRECISE score, is associated with functional outcomes at 90 days after EVT for ACLVO.
Key Words: Thrombectomy—stroke—cerebral veins—large vessel occlusion

Introduction

Endovascular thrombectomy (EVT) has been established as a standard of care for the acute ischemic stroke due to anterior circulation large vessel occlusion (ACLVO). In 2015, 5 randomized controlled trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) showed the benefit of mechanical thrombectomy over the standard medical management.[1-5] Pooled analysis of these trials (HERMES) found that EVT within 12 hours of symptom onset achieves a favorable neurologic outcome (modified Rankin Scale [mRS] of 0-2) in roughly 20% at 90 days.[6] Imaging used to guide treatment for these trials included computed tomographic angiography (CTA) to identify an occlusion in a proximal cerebral artery, and noncontrast computed tomography (CT) to identify at-risk but noninfarcted cortex (the ischemic penumbra) via the Alberta Stroke Program Early CT Score (ASPECTS). More recent trials such as DAWN and DEFUSE 3 used perfusion imaging in conjunction with automated software to better characterize the ischemic penumbra.[7,8] They also demonstrated the efficacy of EVT up to 24 hours after symptom onset. Despite the fact that patients in the latter trials had a much longer time from symptom onset to reperfusion, a greater proportion of these patients were functionally independent at 90 days

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(49% and 45%, respectively).[7,8] This so-called late window paradox likely reflects the ability to select for patients with a relatively small core infarct and favorable collaterals that stall the loss of the penumbra by using perfusion imaging.[9]

Cortical venous opacification on CTA is another potential means to assess the tissue state and extent of collateral circulation for patients with ACLVO. Two recent studies have explored this possibility, each with its own scoring system.[10,11] The Prognostic Evaluation based on Cortical vein score difference In Stroke (PRECISE) study found that decreased opacification of the cortical veins in the affected hemisphere compared to the unaffected hemisphere was predictive of poor outcome (mRS 3-6).[11] The Cortical Vein Opacification Score (COVES) study was a larger retrospective study using data from MR CLEAN. This group found that the absence of cortical venous opacification in the affected hemisphere was not only associated with poor outcomes but also a lack of benefit from EVT when compared to a control group.[10]

The availability of additional factors for identifying patients who are more likely to benefit from EVT is desirable. Although ASPECTS and CT perfusion provide valuable information regarding the presence of salvageable tissue, assessment of venous opacification may augment this by indicating the resistance of the microcirculatory bed in the affected vascular territory. The COVES and PRECISE scores differ both in the veins they evaluate and the manner in which they are calculated. To date, the 2 scores have not been directly compared, and their predictive abilities have only been evaluated in the studies introducing them. As a result, their use in clinical practice remains limited. Our study aimed to assess and compare the sensitivity and specificity of the PRECISE and COVES scores for predicting functional outcomes after EVT for ACLVO in our own retrospective cohort.

Materials and Methods

Patient Selection

After obtaining Institutional Review Board approval (#962789-4), a retrospective review was performed identifying all patients at our institution who received EVT for ACLVO between January 1, 2014 and December 25, 2017. Inclusion criteria included the availability of pre-procedural CTA and confirmation of ACLVO as defined by occlusion of the internal carotid artery or proximal middle cerebral artery (M1 or proximal M2) on digital subtraction angiography. The electronic medical record was reviewed for patient characteristics and clinical outcomes. Patient characteristics included age, sex, presence of hypertension, diabetes mellitus, or hyperlipidemia, National Institutes of Health Stroke Scale (NIHSS), administration of intravenous (IV) tissue plasminogen activator (tPA), imaging characteristics, and complications including symptomatic intracranial hemorrhage (sICH) and cerebral infarction.

Venous Opacification Scores

A single observer who was blinded to clinical outcomes calculated the PRECISE and COVES scores using the methodology described in the original studies.[10,11] PRECISE scores ranged from 0 to 8 and a score of 0-3 was considered favorable (Table 1). This score was obtained by assessing contrast filling as absent (0), partial (1), or full (2) for the superficial middle cerebral vein (SMCV), vein of Labbé (VOL), vein of Trolard (VOT), and basal vein of Rosenthal (BVR) in each hemisphere. The contrast filling score for the hemisphere ipsilateral to the occlusion was subtracted from that of the contralateral normal hemisphere. Contrast had to fill the vein for at least one-third of its course from its origin in order to be counted.

Table 1. *Comparison of the cortical vein opacification score (COVES) and the prognostic evaluation based on cortical vein score difference in stroke (PRECISE) score*

	COVES	PRECISE
Superficial middle cerebral vein (SMCV)	Yes	Yes
Vein of Labbé (VOL)	Yes	Yes
Sphenoparietal sinus (SPS)	Yes	No
Vein of Trolard (VOT)	No	Yes
Basal vein of Rosenthal (BVR)	No	Yes
Assessment of contrast filling	Full = 2 Partial = 1 Absent = 0	Full = 2 Partial = 1 Absent = 0
Calculation	$SMCV_{ips} + VOL_{ips} + SPS_{ips}$	$(SMCV_{cont} + VOL_{cont} + VOT_{cont} + BVR_{cont})$ - $(SMCV_{ips} + VOL_{ips} + VOT_{ips} + BVR_{ips})$
Range of possible scores	0-6	0-8
Range of favorable scores	1-6	0-3

Abbreviations: cont, contralateral to occlusion; ips, ipsilateral to occlusion.

COVES scores ranged from 0 to 6 and a score greater than 0 was considered favorable (Table 1). This score was obtained by assessing venous opacification as absent (0), partial (1), or full (2) for the SMCV, VOL, and the sphenoparietal sinus (SPS) for the hemisphere ipsilateral to the occlusion. The timing of images in this study was considered adequate if one of either sigmoid sinus jugular bulbs was opacified by contrast.

Outcomes

Our primary clinical outcome was the mRS score at 90 days. A favorable mRS score was defined as 0 (no disability)-2 (slight disability), whereas a score of 3 (moderate disability)-6 (mortality) was considered unfavorable. Other outcomes of interest included mortality at 90 days, Thrombolysis in Cerebral Infarction (TICI) Score, and the presence of sICH. TICI scores of 2B or 3 were considered favorable.

Statistical Analysis

Univariate analysis was performed using Mann-Whitney *U* test for continuous variables and X^2 test for categorical variables. Binary logistic regression analysis was used to identify whether COVES or PRECISE scores were associated with the primary clinical outcome, adjusting for age, NIHSS on admission, TICI score, time to reperfusion, and the administration of IV tPA. The same analysis was performed without dichotomizing the 90-day mRS score using multinomial logistic regression. Receiver operating characteristic (ROC) curves were generated to evaluate the PRECISE and COVES scores' abilities to differentiate favorable and unfavorable outcomes. Statistical analysis was performed with IBM SPSS Statistics 24.0 (IBM Corp., Armonk, NY).

Results

Demographic and Presenting Data

From 2014 to 2017 a total of 369 patients received EVT for proximal anterior circulation stroke. There were 103 patients with preprocedural CTA available to evaluate venous opacification, and these patients were included in the study. Those without CTA had imaging from an outside hospital that was not available (155), did not receive CTA due to hyperdense MCA sign on noncontrast CT (89), or had preprocedural MR angiography instead of CTA (22). Inclusion and exclusion of patients in this study are represented in Figure 1.

Our cohort had an average age of 68.3 years ($\sigma = 15.9$) and was predominantly male (84.5% male). In terms of comorbidities, 74.8% had hypertension, 17.5% had diabetes mellitus, and 46.6% had hyperlipidemia. The median NIHSS on admission was 15 (interquartile range: 10-18). Approximately half (50.5%) of the patients in our cohort received IV tPA prior to EVT. The mean time to reperfusion was 6.4 hours ($\sigma = 3.9$). Table 2 describes these patient characteristics stratified by favorable and unfavorable COVES and PRECISE venous opacification scores.

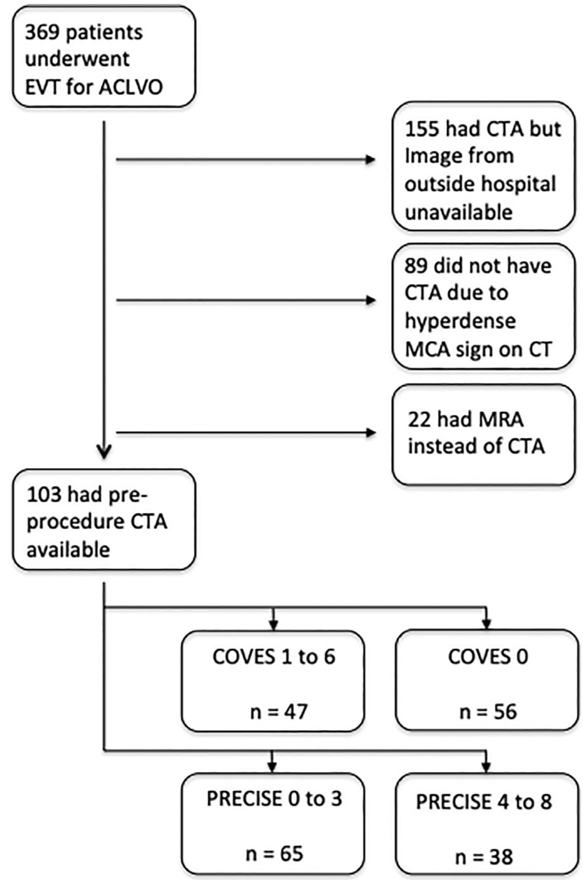

Figure 1. *Patient flow through the study. A total of 103 patients met inclusion criteria.*

Predictors of Clinical Outcomes

Overall, EVT successfully achieved TICI 2B or 3 reperfusion in 77.7% of cases. Favorable neurologic outcomes, as defined by a mRS of 0-2 at 90 days, were achieved in 46.6% of patients. The mortality rate at 90 days was 25.2% for the entire cohort. The incidence of sICH was 21.4%. Table 3 describes the associations between various preprocedural and procedural characteristics as well as the COVES and PRECISE scores with clinical outcomes in a binomial logistic regression. The model was statistically significant ($X^2(7) = 24.9$, $P = .001$) and the Hosmer-Lemeshow test indicated that the data fit the model well ($P = .409$). The adjusted odds ratio (aOR) reflects multivariate logistic regression analysis adjusting for age, NIHSS on admission, TICI score, time to reperfusion, and administration of IV tPA. A favorable COVES score was associated with favorable mRS (aOR: 4.78; 95% CI 1.73-13.22) but a favorable PRECISE score was not. Figures 2 and 3 illustrate the distribution of mRS scores at 90 days based on the COVES and PRECISE scores, respectively. As shown in Table 4, an unfavorable COVES score was

Table 2. *Univariate analysis of patient characteristics stratified by venous opacification score*

	COVES Favorable (%)	COVES Unfavorable (%)	p	PRECISE Favorable (%)	PRECISE Unfavorable (%)	p
Number of patients	47	56	-	65	38	-
Mean age (years)	67.6	68.9	.547	70.2	65.2	.119
Median NIHSS on admission	15	15	.529	14	16	.805
Received IV tPA	24 (51.1)	28 (50.0)	.914	37 (56.9)	15 (39.5)	.087
Mean time to reperfusion (hours)	6.2	6.5	.208	6.3	6.5	.796
Favorable TICI	39 (83.0)	41 (73.2)	.236	54 (83.1)	26 (68.4)	.085

Abbreviations: COVES, Cortical Vein Opacification Score; NIHSS, National Institute of Health Stroke Scale; PRECISE, Prognostic Evaluation based on Cortical vein score difference In Stroke; TICI, thrombolysis in cerebral infarction; tPA, tissue plasminogen activator.

Table 3. *Proportion of favorable outcomes based on preprocedural and procedural characteristics*

	Favorable mRS (%)	Unfavorable mRS (%)	aOR (95% CI)	p
Mean age (years)	64.4	71.7	.98 (.95-1.00)	.093
Mean time to reperfusion (hours)	7.0	5.9	1.07 (.95-1.21)	.282
Favorable TICI	40 (83.3)	40 (72.7)	2.13 (.68-6.61)	.192
Median NIHSS	13	16	.92 (.85-.99)	**.029**
IV tPA administered	22 (45.8)	30 (54.5)	.77 (.30-1.97)	.580
Favorable COVES	30 (62.5)	17 (30.9)	4.78 (1.73-13.22)	**.003**
Favorable PRECISE	33 (68.8)	32 (58.2)	.90 (.31-2.59)	.841

Abbreviations: COVES, Cortical Vein Opacification Score; mRS, Modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PRECISE, Prognostic Evaluation based on Cortical vein score difference In Stroke; TICI, thrombolysis in cerebral infarction; tPA, Tissue plasminogen activator.

associated with poor mRS (aOR: 3.06; 95% CI 1.15-8.13) but an unfavorable PRECISE score was not (aOR: 1.02; 95% CI .37 − 2.80). In the multinomial regression analysis performed using nondichotomized 90-day mRS scores, a favorable COVES score was associated with higher odds of each favorable mRS: mRS 0 (aOR: 5.68; 95% CI 1.12-28.82), mRS 1 (aOR: 7.53; 95% CI 1.36-41.66), and mRS 2 (aOR: 7.60; 95% CI 1.88-30.67). A favorable PRECISE score was associated with a mRS of 1 (aOR: 11.23; 95% CI 1.53-82.21), but none of the other 90-day mRS scores in the multinomial regression.

Comparison of COVES and PRECISE Scores

We directly compared the prognostic value of the COVES and PRECISE scores by several measures. The 2 scores predicted the same clinical outcome, whether favorable or unfavorable, in 71 (68.9%) of our cases. This resulted in a

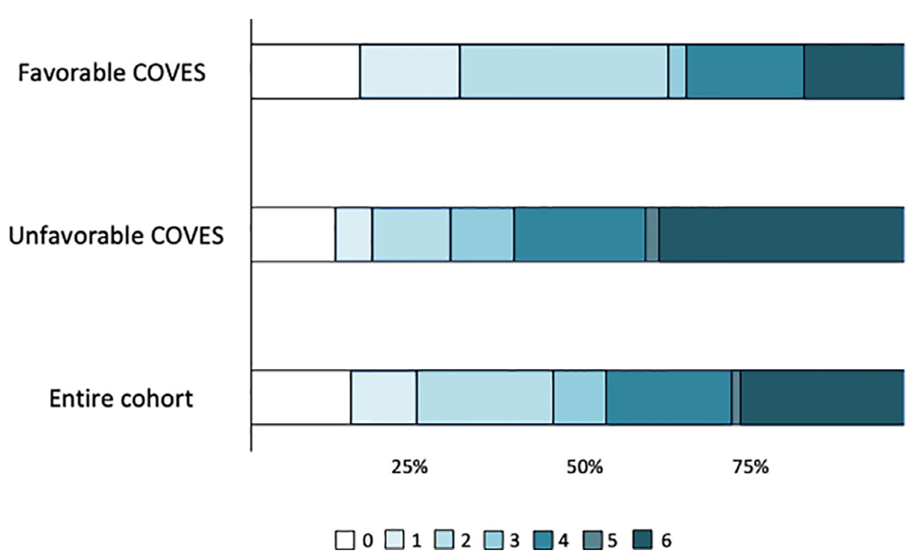

Figure 2. *Distribution of modified Rankin Scale scores stratified by COVES score. Abbreviation: COVES, Cortical Vein Opacification Score.*

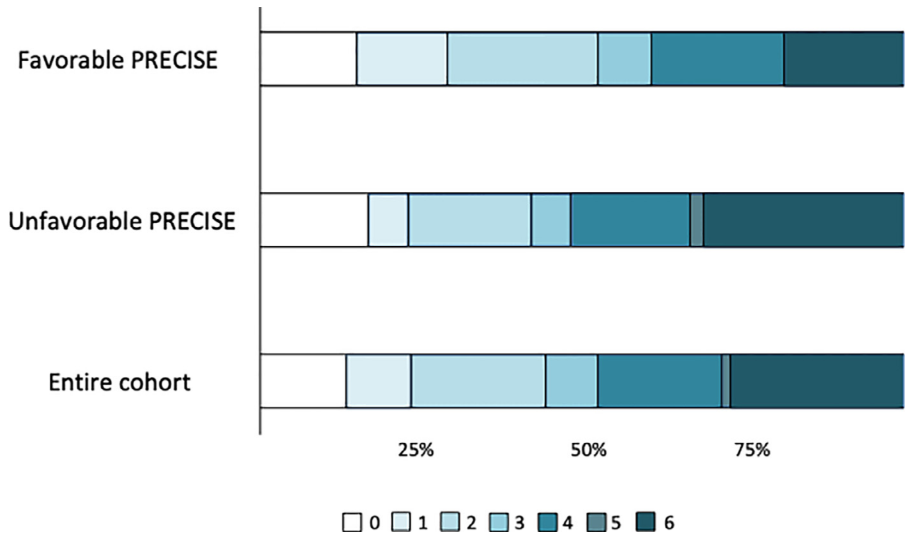

Figure 3. *Distribution of modified Rankin Scale scores stratified by PRECISE score. Abbreviation: PRECISE, Prognostic Evaluation based on Cortical vein score difference In Stroke.*

Cohen's kappa coefficient of .39 (95% CI .23-.56). We performed a ROC analysis for each of the scores. The COVES score had a sensitivity of 68.1%, specificity of 71.4%, and an area under the curve (AUC) of .77 for predicting a favorable outcome. The optimal cut-off point was between a COVES score of 0 and 1. The PRECISE score had a sensitivity of 68.9%, specificity of 70.7%, and an AUC of .73 for predicting a favorable outcome. The optimal cut-off point was between a PRECISE score of 3 and 4. The results of our ROC analyses are demonstrated in Figure 4.

Illustrative Case

A 76-year-old male presented with acute left hemiparesis and a NIHSS of 5. CTA performed 11 hours after symptom onset revealed a right M1 occlusion with an ASPECTS score of 6. CTA also showed absent filling of the ipsilateral SMCV, VOL, and SPS, yielding an unfavorable COVES score of 0. There was complete filling of the contralateral VOT and partial filling of the contralateral SMCV, VOL, and BVR. Ipsilateral to the occlusion there was partial filling of the VOT and BVR (Fig 5). Therefore, he had a favorable PRECISE score of 3. Mechanical thrombectomy was performed with TICI III recanalization. The time from symptom onset to reperfusion was 14 hours. The patient was discharged to inpatient rehabilitation but ultimately had an unfavorable 90-day mRS of 4.

Discussion

The use of mechanical thrombectomy for large vessel stroke continues to expand as more trial data becomes available and patient selection criteria are continually refined. The 2018 American Heart Association/American Stroke Association guidelines extended the therapeutic window of EVT to 24 hours, which reflected the added value of perfusion imaging-based selection as demonstrated in the DAWN and DEFUSE 3 trials.[12] One study found that ASPECTS score and an arterial collateral score could be used to predict perfusion profiles at less than 12 hours without using perfusion imaging.[13] There remains a need for additional ways to predict which patients are most likely to benefit from EVT, as currently less than half of patients (range: 45%-49%) undergoing EVT for ACLVO reach functional independence.[6-8]

Historically, leptomeningeal arterial branches have received the most attention in evaluating collateral circulation, but venous opacification on CTA could provide additional prognostic value without the need for additional imaging. The extent and velocity of cortical venous filling

Table 4. *Clinical outcomes by venous opacification score*

	Favorable COVES (%)	Unfavorable COVES (%)	aOR (95% CI)	*P*	Favorable PRECISE (%)	Unfavorable PRECISE (%)	aOR (95% CI)	*P*
Unfavorable mRS	17 (36.2)	38 (67.9)	3.06 (1.15-8.13)	**.025**	32 (49.2)	23 (60.5)	1.02 (.37-2.80)	.966
Mortality	7 (14.9)	19 (33.9)	1.44 (.45-4.59)	.536	13 (20.0)	13 (34.2)	1.98 (.66-5.95)	.224
Symptomatic ICH	8 (17.0)	14 (25.0)	1.23 (.44-3.45)	.699	11 (16.9)	11 (28.9)	1.91 (.71-5.12)	.200

Abbreviations: COVES, Cortical Vein Opacification Score; ICH, intracerebral hemorrhage; mRS, Modified Rankin Scale; PRECISE, Prognostic Evaluation based on Cortical vein score difference In Stroke.

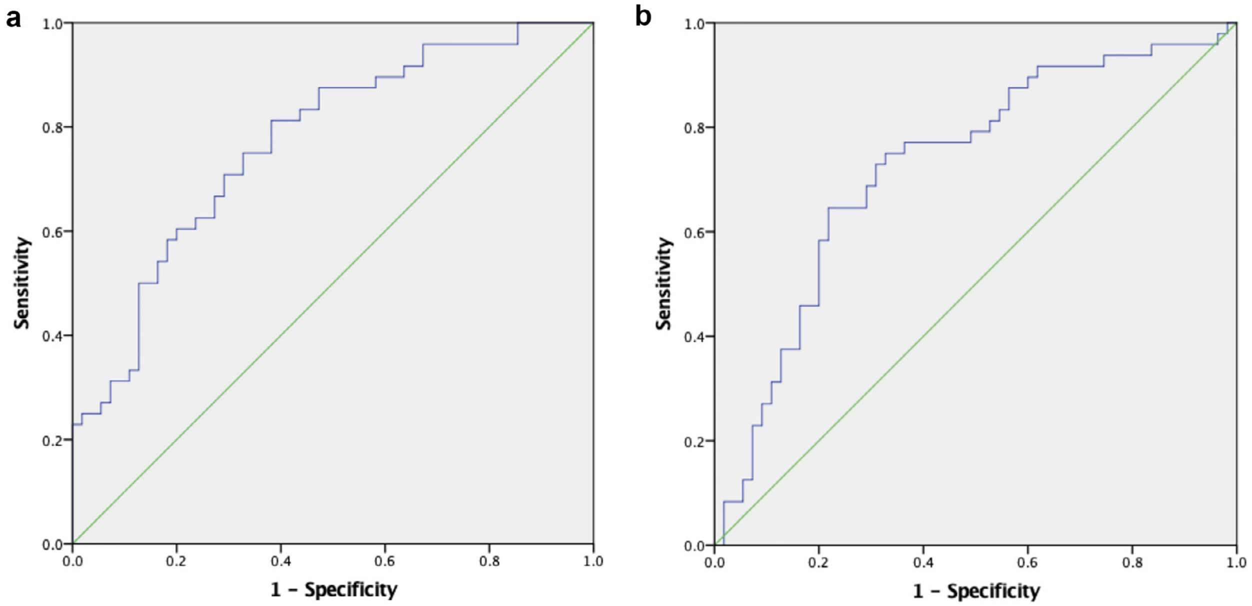

Figure 4. *Receiver operating characteristic curves for (a) COVES and (b) PRECISE to distinguish between favorable and unfavorable modified Rankin Scale scores. The AUC for the COVES and PRECISE scores were .77 and .73, respectively. Abbreviations: AUC, area under the curve; COVES, Cortical Vein Opacification Score; PRECISE, Prognostic Evaluation based on Cortical vein score difference In Stroke).*

has been associated with clinical outcomes in patients with ACLVO.[14,15] Less extensive cortical venous filling may correlate with poor collateral circulation, increased microcirculatory resistance, and also to the presence of microthrombi in the venules of affected territories.[16,17] The COVES and PRECISE scores both assess venous opacification, but the predictive values of these scores have not been compared. The use of multiple scores for venous opacification in clinical practice would likely be prohibitively time-consuming, underscoring the importance of establishing and comparing each one's predictive abilities.

We found a significant association between the COVES score and functional outcome at 90 days. It was able to predict both unfavorable and favorable outcomes. Conversely, no such association between PRECISE score and functional outcome was observed. Similar to the original study, we found that the optimal cutoff for distinguishing a poor PRECISE score from a favorable one was 4 or greater.[11] The authors of the PRECISE score first reported that interhemispheric difference in venous contrast filling had a relatively strong association (aOR 23.598, $P = .009$) with poor outcome after adjusting for ASPECTS, CTA collateral grade, and NIHSS on admission.[11] In our cohort, however, this association was not present.

We found that the COVES score, as reported in its initial study,[10] did have a statistically significant association with 90 day functional outcomes. In our cohort this effect was slightly stronger than in the original study (aOR 3.06 versus aOR 2.2, respectively).[10] Similar to the original study, we found that the optimal cutoff for distinguishing favorable from unfavorable outcomes was a COVES score of 1 or greater.[10] The COVES score had similar sensitivity (68.1% versus 68.9%) and specificity (71.4% versus 70.7%) for predicting mRS at 90 days as the PRECISE score in our

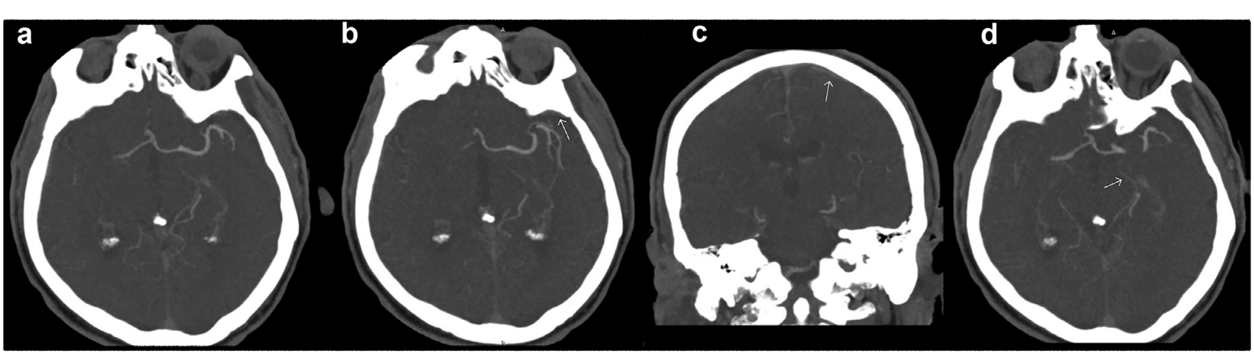

Figure 5. *(a) CTA demonstrating right M1 occlusion in the case described. There was partial filling of the contralateral superficial middle cerebral vein (b), complete filling of the contralateral vein of Trolard (c), and partial filling of the contralateral basal vein of Rosenthal (d). Arrows indicate the described contralateral veins. Partial filling of the ipsilateral vein of Trolard and basal vein of Rosenthal were present. Abbreviation: CTA, computed tomography angiography.*

cohort. The AUC for the COVES score was .77 versus .73 for the PRECISE score. This comparison is similar to that seen in a follow-up evaluation of the PRECISE score by its original authors; the interhemispheric PRECISE score had a slightly lower performance (AUC .807) when compared to the composite venous opacification score of only the ipsilateral hemisphere (AUC .824).[18] Assuming no heterogeneity between the study cohorts, the lower performance of the PRECISE score may reflect the normally occurring variability of the superficial cerebral veins.[19] Another possibility is differing prognostic significance of the SPS versus that of the BVR and VOT. Isolated striatocapsular infarcts (a territory drained by the BVR) following EVT, for example, have been shown to have relatively little impact on neurologic outcomes as measured by mRS.[20]

Both the COVES and PRECISE studies are limited by the size of their cohort and the exclusion of a large number of patients, primarily due to the timing of contrast administration. In the COVES study, 216 patients were included who underwent intervention, while 101 were excluded.[10] In the PRECISE study, the total cohort size was only 39 patients and the number of patients excluded was not mentioned.[11] The previously mentioned follow-up study that revisited the PRECISE score included 81 and excluded 119.[18] We also were forced to exclude a large number of patients due to lack of preprocedural CTA. However, our cohort of 103 patients is the largest application of the PRECISE score in the literature and is the first comparison of these 2 scores.

Limitations of our study include the retrospective nature of our analysis and lack of a control group. One individual performed all grading of venous opacification, which likely increased the reliability of our calculated COVES and PRECISE scores. However, these conditions may not reflect their application and performance in clinical practice. Additionally, venous opacification is affected by imaging protocols, including the time and rate of contrast injection. Calculation of the COVES and PRECISE scores could have also been affected by slice thickness and the number of slices available for review. Multiple protocols were used for the images in our study due to the change in these protocols over the period studied (4 years) and due to the transfer of patients to our institution for stroke intervention. Of note, the COVES and PRECISE scores do not apply to posterior circulation, small vessel, or anterior cerebral artery strokes, which will limit their implementation in clinical practice. Other clinical and radiographic data will be required to determine whether or not to pursue EVT in these settings.

Despite these limitations, the results of our study and of the COVES, PRECISE, and other analyses point to cortical venous opacification as a predictor of clinical outcomes after ACLVO.[10,11,14,15,17,18] Whether or not it is an independent predictor requires direct comparison to other methods of predicting clinical outcome, which we did not perform. Likewise, larger studies with prospective application of these scores and appropriate controls would be useful in confirming the utility of cortical venous opacification and the COVES and PRECISE scores in patient selection for EVT. These scores may be the most useful for aiding in patient selection in the early therapeutic window, when perfusion imaging is not currently recommended.[12] They may also be helpful as adjuncts to the standard CT perfusion-based decision-making protocols to more reliably predict who will benefit from the intervention. Our data suggest that COVES is more strongly associated with outcomes than the PRECISE. The COVES score may enhance the decision-making process when deciding whether or not to pursue EVT for ACLVO. However, large prospective comparative studies are needed to (1) definitively establish any superiority of one venous opacification score over the other, (2) determine whether or not the COVES score increases the ability to predict clinical outcomes when applied with other methods that attempt the same goal (i.e., ASPECTS score), and (3) identify how to handle discordant results when using the COVES score with other predictive measures.

Conclusions

Poor cortical venous opacification, as defined by an unfavorable COVES score, was associated with unfavorable neurologic outcomes at 90 days in our retrospective cohort of patients undergoing EVT for ACLVO. Furthermore, favorable COVES scores were associated with favorable 90-day functional outcomes. We believe that this scoring system has a useful adjunctive role in patient selection for mechanical thrombectomy, particularly in the early therapeutic window. However, a prospective multicenter study is needed to confirm the prognostic ability of cortical venous opacification scoring systems.

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