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Comprehensive venous outflow is the optimal venous score in predicting functional outcome in acute ischemic stroke patients

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Abstract

Background: Venous outflow (VO) is a promising prognostic imaging biomarker in acute ischemic stroke (AIS) patients selected for endovascular treatment (EVT). However, the best score for properly assessing VO profiles on multi-phase CT-Angiography (mCTA) remains to be identified.

Methods: A series of consecutive AIS patients undergoing EVT for large vessel occlusion within 24 h from symptom onset were investigated. The following scores were rated: cortical vein score difference in stroke (PRECISE, range 0–8), cortical vein opacification score (COVES, range 0–6), comprehensive venous outflow (CVO, range 0–8) and internal cerebral vein (ICV) asymmetry. Receiver operating characteristic curves and multivariable logistic regression analyses were performed to explore the performance of the different VO scores for prediction of a good outcome (modified Rankin Scale 0–2 at 3 months).

Results: Three hundred and thirty-six subjects (56.2% females, mean age 74.8) were included, of whom 145 (43.1%) had good outcomes. In multivariable logistic analysis, the CVO score (odds ratio = 2.51, 95% CI = 1.49–4.18, $p = .001$) was the only independent predictor of good functional outcomes. The AUC of the CVO score was .75 (95% CI = .70–.80), with an optimal cut-off of ≥4 (sensitivity 56%, specificity 69%). Patients with favourable CVO profiles had better pial arterial (70.7%, $p < .001$) and hypoperfusion intensity ratio (HIR) tissue-related collaterals (HIR = .35, $p = .005$), higher rates of successful recanalization (95.7%, $p < .001$) and lower symptomatic intracranial haemorrhage occurrence (6%, $p = .020$) than those with unfavourable CVO profiles.

Conclusion: The CVO score measured on mCTA had the best discriminative performance and was independently associated with functional outcome in AIS patients undergoing EVT within 24 h from onset.

KEYWORDS
acute ischemic stroke, cortical vein opacification score, endovascular treatment, hypoperfusion intensity ratio, multiphase CT-angiography, venous outflow

1 | INTRODUCTION

Endovascular treatment (EVT) is the recognized standard of care in acute ischemic stroke (AIS) patients suffering from large vessel occlusion (LVO) presenting within 24 h from symptom onset.[1] However, despite successful recanalization, about half of patients undergoing EVT experienced poor clinical outcomes.[2] Heterogeneity in collateral flow, a well-known key factor in predicting good functional outcomes, might explain the high rate of futile recanalization.[3] Collaterals consist of a network of arteries across different brain regions allowing to preserve blood flow in case of vessel occlusion and sustaining cerebral perfusion over time, particularly in the tissue at risk of infarction, namely penumbra.[3] Nonetheless, adequate brain perfusion of ischemic territories relies not only on the inflow of arterial vessels but also on blood outflow into cerebral veins.[4] Consistently, poor venous drainage seems to lead to the impairment of leptomeningeal blood flow and hindered blood passage into the ischemic tissue.[5] Moreover, high edema formation and futile recanalization have been demonstrated in subjects with an ineffective venous system.[6,7] Therefore, a growing body of evidence has suggested that the assessment of venous outflow (VO) could be a promising imaging biomarker to improve patient selection for reperfusion therapies as subjects with favourable VO profiles were proved to achieve good clinical outcomes after EVT.[3–8] Thus, several scores have been proposed to evaluate venous filling but which of these grading systems had the higher ability to identify patients who actually can benefit from EVT remains to be clarified since in each score different venous structures were evaluated.[8] In particular, medullary vein (MV)[9] and internal cerebral vein (ICV)[10] asymmetry was adopted to assess deep venous drainage, COVES (cortical vein opacification score)[11] and TVS (total venous score)[12] for evaluating superficial venous drainage and, finally, PRECISE (prognostic evaluation based on cortical vein score difference in stroke)[13] and CVO (comprehensive venous outflow)[14] for both deep and cortical VO assessment. However, MV asymmetry has been recently indicated as a more reliable imaging biomarker for the prognosis of AIS patients with small vessel occlusion[15,16] or subjects with subacute stroke,[17] since MV represents the principal drainage of deep white matter territories. In addition, no association was proved between TVS score and dichotomous modified Rankin Scale (mRS) 0–2 at 3 months or major clinical improvement.[12] As a result of these observations, PRECISE, COVES, CVO and ICV scores have been recognized as the most accurate grading systems to define a favourable VO profile.[8] However, the diagnostic performance of different scores has not been systematically evaluated and most of the available evidence was derived from sCTA[11,13,14] that has probably a lower accuracy compared to mCTA.[18] The aim of our study was therefore to compare different VO scores evaluated on mCTA to predict functional outcomes in AIS patients undergoing endovascular treatment.

2 | METHODS

This cohort study was approved by the local ethics boards and clinical information was recorded during routine clinical activity. Written informed consent was obtained from each patient or from their legally authorized representatives at admission.

2.1 | Patient selection

We retrospectively analysed a prospectively collected cohort of 336 consecutive AIS patients with anterior circulation LVO treated with EVT and admitted from January 2020 to December 2023 at our Hospital. All patients presenting with suspected AIS with LVO underwent noncontrast CT (NCCT), mCTA of the cervical and intracranial vessels and CT perfusion (CTP) at admission within 24 h of symptom onset. Patients were included if they presented to the emergency department with the following criteria: (1) diagnosis of AIS within 24 h from witnessed symptom onset or time last seen well; (2) evidence of middle cerebral artery (MCA) M1 segment occlusion, M2 segment MCA occlusion or internal cerebral artery (ICA) occlusion on CTA; (3) selected for receiving EVT; and (4) follow-up NCCT imaging performed at 24 ± 12 h. Exclusion criteria were as follows: (1) age < 18 years; (2) pregnancy; (3) severe pre-stroke disability defined as modified Rankin Scale (mRS) ≥ 3; (4) detection of intracerebral haemorrhage (ICH) on admission NCCT; (5) contraindications to iodinated contrast agent; (6) poor quality of CT acquisition due to motion artefacts; (7) inability to complete

the multi-modal CT protocol or the conventional digital subtraction angiography (DSA) study at baseline and/or 24-h follow-up NCCT.

2.2 | Clinical assessment

Clinical, demographic and technical data were collected by trained investigators blinded to the outcomes of interest, from the patient's medical records and a prospectively maintained institutional stroke database, including age, sex, pre-stroke functional status (mRS), the presence of stroke risk factors, the interval between symptom onset and neuroimaging, the initial National Institute of Health Stroke Scale (NIHSS) score, the use of intravenous thrombolysis (IVT) and EVT. Clinical outcome was measured using the mRS at 3 months. Good outcome was defined as mRS 0–2 at 3 months. The mRS was evaluated by trained investigators, blinded to all imaging findings.

2.3 | Imaging acquisition

All imaging protocol was conducted on a 128-slice scanner (Philips Brilliance iCT, Best, the Netherlands). NCCT helical scans were performed from the skull base to the vertex using the following imaging parameters: 120 kV, 340 mA, .6 collimation, 1 s/rotation and table speed of 15 mm/rotation. mCTA was performed as follows: the first phase (peak arterial phase) of the cervical and intracranial vessels covered from the aortic arch to the vertex using .7 mL/kg contrast (maximum 90 mL), 5- to 10-s delay from injection to scanning, 120 kV, 251 mAs, .75 s/rotation, .8/.4 mm thick slices (imbricated slices), scan time 4 s. The second phase (peak equilibrium/peak venous phase) and third phase (late venous phase) were acquired from the skull base through the vertex after a delay of 4 s that allows for table repositioning to the skull base. Scanning duration for each additional phase was 3.4 s. The axial images were reconstructed at .4-mm overlapping sections, and MIP multiplanar reconstructions for axial, coronal, and sagittal images of the circle of Willis were performed with 10 mm thickness at 3 mm intervals. CTP studies were obtained with a dynamic first-pass bolus-tracking methodology according to a 2-phase imaging protocol, to avoid the truncation of time density curves, with toggling table technique. The 2-phase acquisition consisted of a first phase every 3.2 s for 60 s and an additional second phase every 15 s for 113 s, which started 5 s after the automatic injection of 40 mL of nonionic contrast agent followed by a saline flush of 40 mL at the rate of 4 mL/s. Sections of 8 cm length (across z axis) were acquired at 5 mm slice thickness. The other acquisition parameters were 80 kV, 150 mAs, and .33 rotation time. All CTP source images were reconstructed with a standard filter and display field of view (DFOV) of 25 cm.

2.4 | Imaging processing and analysis

Figure 1 shows the imaging processing pipeline. The extent of early ischemic changes was evaluated on baseline NCCT using the ASPECTS methodology.[19] Occlusion sites were identified on mCTA and classified as terminal ICA, MCA-M1 segment or MCA-M2 segment occlusions. mCTA and VO scores were independently graded by two neuroradiologists, (with more than 10 and more than 20 years of experience, respectively), both blinded to clinical information. Inter-reader agreement among these two neuroradiologists for the assessment of acute stroke imaging features using multimodal imaging in this cohort was previously evaluated and demonstrated excellent reliability, with Cohen's kappa coefficient >.8.[20] Discrepancies were discussed and resolved by a consensus reading. mCTA collateral supply was graded on a 6-point scale according to a previously published scoring system.[21] Grades 0–3 were classified as poor and grades 4–5 as good collaterals. As it was previously demonstrated that the second phase was the best for estimating VO with mCTA,[18] all venous outflow scores were evaluated on the peak venous phase of mCTA by assessing contrast filling as absent (0), partial (1) or full (2) by comparing the affected side with the contralateral healthy side. Venous drainage structures taken into account and the grading scales for each score are summarized in Table 1. Favourable VO profiles were defined according to previously published thresholds for PRECISE,[11] COVES,[13] CVO[14] and ICV[9] scores. CTP study was processed by commercially available delay-insensitive deconvolution automated software (Olea Sphere Version 3.0 SP23; Olea Medical, La Ciotat, France), using the standard singular value decomposition method according to manufacturer instructions. All steps, including motion correction, smoothing and evaluation of time density curves, selection of arterial input and venous output functions, were checked for errors. As recommended by the vendor, total hypoperfused tissue and ischemic core volumes were defined as ischemic brain regions with time-to-maximum (Tmax) threshold values >6 s (Tmax >6 s) and relative cerebral blood flow (rCBF) threshold values less than 40% of normally perfused tissue (rCBF <40%), respectively. The difference between the extent of Tmax >6 s lesion and rCBF <40% lesion size was considered as ischemic penumbra. Mismatch ratio was defined as the Tmax >6 s volumes divided by rCBF <40% volumes. All these parameters

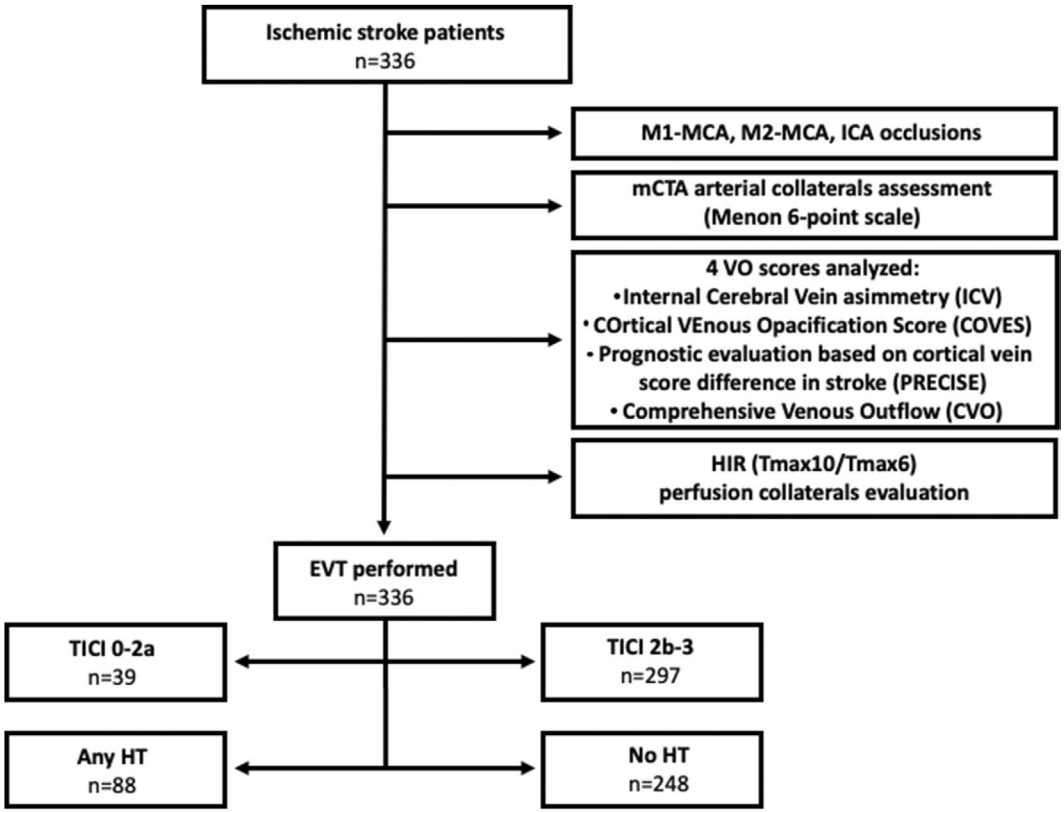


FIGURE 1 Patient population imaging processing pipeline. EVT, endovascular treatment; HIR, hypoperfusion intensity ratio; HT, hemorrhagic transformation; ICA, internal cerebral artery; MCA, middle cerebral artery; mCTA, multiphase CT-angiography; mTICI, modified treatment in cerebral infarction.

TABLE 1 Comparison of the prognostic evaluation based on cortical vein score difference in stroke (PRECISE), cortical vein opacification (COVES) and comprehensive venous outflow (CVO) scores.

	PRECISE score	COVES score	CVO score
Venous drainage			
Sphenoparietal sinus (SPS)	Not	Evaluated	Evaluated
Vein of Labbè (VOL)	Evaluated	Evaluated	Evaluated
Superficial middle cerebral vein (SMCV)	Evaluated	Evaluated	Evaluated
Basal vein of Rosenthal (BVR)	Evaluated	Not	Not
Vein of Trolard (VOT)	Evaluated	Not	Not
Internal cerebral vein (ICV)	Not	Not	Evaluated
Score evaluation			
Assessment of contrast filling	Full = 2, partial = 1, none = 0	Full = 2, partial = 1, none = 0	Full = 2, partial = 1, none = 0
Grading score range	0–8	0–6	0–8
Favourable venous profile	0–3	3–6	4–8

were automatically segmented and calculated by the software. The hypoperfusion intensity ratio (HIR) was defined as the ratio between Tmax >10-s and Tmax >6-s lesion volumes, with HIR values <.4 predicting good tissue-related collaterals.[20] Recanalization rate was assessed on DSA at the end of the EVT procedure using the modified treatment in cerebral ischemia (mTICI). Patients with an mTICI score of 2b–3 were considered as successfully recanalized, whereas patients with an mTICI score ranging from 0 to 2a were classified as not.[22] Hemorrhagic Transformation (HT) was classified on NCCT at 24 h from symptom onset/last known well according to the European Cooperative Acute Stroke Study (ECASS)-II criteria into four different categories:

hemorrhagic infarction type 1 (HI1), HI type 2 (HI2), Parenchymal haemorrhage type 1 (PH1) and PH type 2 (PH2).[23] sICH was defined as any apparently extravascular blood in the brain or within the cranium that was associated with clinical deterioration, as defined by an increase of 4 points or more in the score on the NIHSS, or that led to death and that was identified as the predominant cause of the neurologic deterioration.[24] Follow-up infarct volumes were manually traced using ITK-SNAP software on NCCT at 24 h after symptom onset/last known well by operators blinded to EVT result and clinical outcomes. Final infarct volumes were automatically calculated by this software with a multislice planimetric method by summation of the hypodense areas, manually traced on each slice in which they were detectable, multiplied by slice thickness.[25]

2.5 | Statistical analysis

Dichotomic data were presented as count (%), whereas continuous variables were summarized as mean ± standard deviation (SD) if normally distributed or median and interquartile ranges (IQR) as appropriate. Dichotomous variables were compared using the chi-square test, while continuous variables were compared by Student *T*-test or Mann–Whitney *U*-test as appropriate on the basis of data distribution. The discrimination of PRECISE, COVES, CVO and ICV scores for the identification of patients with good functional outcomes (mRS 0–2) was analysed using area under the curve (AUC) on receiver operating characteristic (ROC) curves and optimal sensitivity, specificity, positive and negative predictive values were identified using the Youden Index. AUC were then compared with the Hanley and McNeil test. Good functional prognosis (defined as mRS 0–2 at 3 months from stroke onset) was the main outcome of interest. Variables associated with good functional outcome were assessed using multivariable logistic regression, adjusting for age, admission NIHSS, pre-stroke disability, ASPECTS score, collateral score, reperfusion status and any variable with $p < .1$ in univariable analysis. Backward elimination was used to reach a final parsimonious model avoiding model overfitting. A subgroup analysis focused on subjects with unsuccessful recanalization (mTICI 0-2a) to test the prognostic performance of all VO scores with the same outcome of interest explored in the main analysis. Furthermore, an interaction term between CVO score and recanalization status (CVO*recanalization status) was created and included in regression analysis to further investigate the relationship between CVO score and good functional outcome. All analyses were performed with the statistical packages SPSS version 25.0 (www.spss.com) and MedCalc (www.medcalc.org). Statistical significance was set at two-sided $p < .05$.

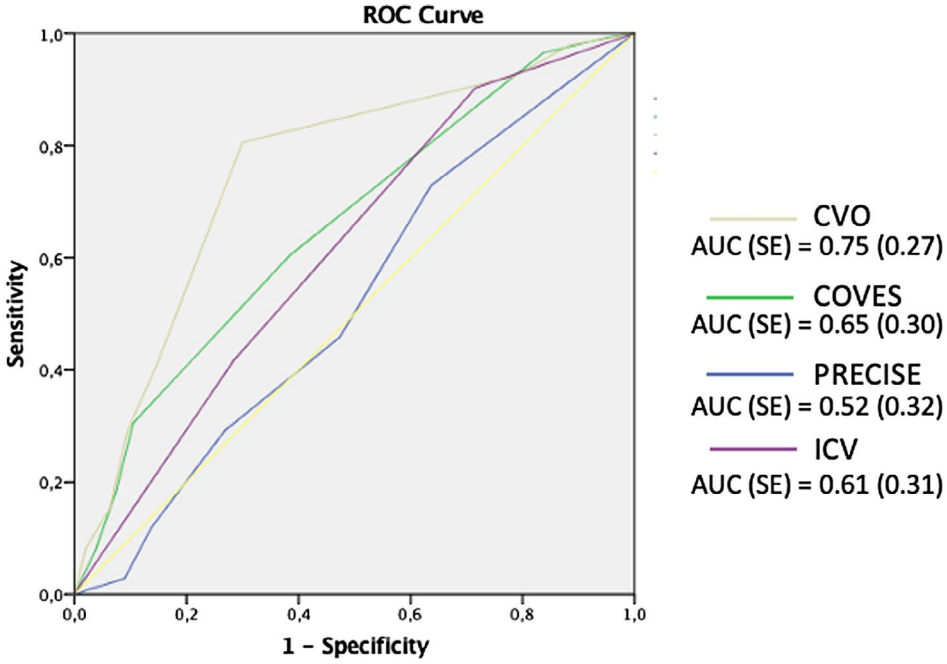
3 | RESULTS

A total of 336 subjects were included (56.2% females, median age 74.8), of whom 145 (43.1%) had good 3-months functional outcomes. Table 2 summarizes the characteristics of patients stratified by functional outcome at 3 months. Most of the included subjects had a middle cerebral artery occlusion in the M1-MCA segment and around one third of patients received TPA before EVT. In univariable analysis, patients with poor outcomes were older, had higher NIHSS and pre-stroke disability on admission. Patients with good clinical outcomes had more favourable VO scores and good mCTA arterial collaterals and showed higher rates of successful recanalization compared to those with poor clinical outcomes. After EVT, patients with favourable outcomes had lower hemorrhagic transformation and symptomatic intracranial haemorrhage incidence, lower NIHSS at discharge and smaller FIV than subjects with unfavourable outcomes. As shown in Figure 2, the ROC curve analysis indicated that the CVO score had the highest discriminative ability for 3-months clinical outcome (AUC .75; 95% CI .45–.58) compared to PRECISE (.52; 95% CI .45–.58), COVES (.65; 95% CI .59–.71) and ICV scores (.61; 95% CI .55–.67). The best cut-off value for predicting favourable outcomes at 3 months was ≤3 for PRECISE, ≥3 for COVES, ≥4 for CVO and ≥1 for ICV. A further prognostic performance analysis (Table S1) on subjects who did not achieve successful recanalization (mTICI 0–2a) showed that CVO still had the higher discriminative ability (AUC .86; 95% CI .74–.99) for predicting favourable outcomes at 3 months. Multivariable logistic regression analysis demonstrated that the CVO was the only VO score independently associated with good clinical outcomes after adjusting for potential confounders (Table 3). In a secondary analysis, an interaction term between CVO and recanalization status was included. The interaction term was not statistically significant ($p > .2$) and its inclusion did not improve the overall performance of the logistic regression model. As illustrated in Table 4, a favourable CVO profile was associated with both good arterial and tissue-related collaterals. Moreover, patients with higher CVO scores achieved higher rates of successful recanalization with lower sICH occurrence as compared to patients with lower CVO scores. Figure 3 shows an illustrative case of a patient experiencing a favourable CVO profile achieving good clinical outcomes with a small follow-up infarct volume.

TABLE 2 Study population characteristics.

Variable	All $n=336$	Good outcome $n=145$	Poor outcome $n=191$	p Value
Age, mean (±SD), years	74.8 (13.5)	72.1 (13.7)	76.8 (13.0)	.004
Sex, woman, *n* (%)	189 (56.2)	79 (54.4)	110 (57.5)	.324
mRS before stroke, median (IQR)	0 (0–2)	0 (0–1)	0 (0–2)	.007
Admission NIHSS, median (IQR)	18 (11–22)	15 (10–20)	19 (14–24)	<.001
ASPECTS, median (IQR)	7 (7–9)	8 (7–9)	7 (5–9)	.138
tPA before EVT, *n* (%)	103 (30.6)	50 (34.4)	53 (27.7)	.161
Onset-to-CT time, min, median (IQR)	380 (210–620)	380 (208–650)	380 (210–620)	.775
Onset-to-CT time <6 h, *n* (%)	157 (46.7)	69 (47.5)	88 (46.1)	
Type of occlusion				
M1-MCA occlusion, *n* (%)	205 (61.1)	84 (57.9)	121 (63.3)	.216
M2-MCA occlusion, *n* (%)	59 (17.5)	32 (22.1)	27 (14.1)	
ICA occlusion, *n* (%)	72 (21.4)	29 (20.0)	43 (22.5)	
Multiphase CT-angiography collaterals				
Poor, *n* (%)	136 (40.5)	39 (26.9)	97 (50.7)	<.001
Good, *n* (%)	200 (59.5)	106 (73.1)	94 (49.3)	
PRECISE score				
0–3, *n* (%)	243 (72.3)	105 (80.6)	138 (65.9)	.001
4–8, *n* (%)	93 (27.6)	40 (19.3)	53 (34.1)	
COVES score				
0–2, *n* (%)	182 (54.2)	64 (44.2)	118 (61.7)	.002
3–6, *n* (%)	154 (45.8)	81 (55.8)	73 (39.3)	
CVO score				
0–3, *n* (%)	172 (51.1)	52 (35.9)	120 (62.8)	.001
4–8, *n* (%)	164 (48.9)	93 (64.1)	71 (37.2)	
ICV score				
0–1, *n* (%)	221 (65.7)	84 (57.9)	137 (71.7)	.008
2, *n* (%)	115 (34.3)	61 (42.1)	54 (28.2)	
rCBF <40% infarct core volume, median (IQR)	30.4 (14.7–52.1)	29.7 (14.7–51.9)	31.5 (14.7–54.2)	.660
Tmax >6-s volume in mL, median (IQR)	102.4 (62.8–148.8)	101.2 (58.2–149.2)	108.4 (65.4–148.8)	.885
Hypoperfusion intensity ratio, median (IQR)	.46 (.22–.51)	.45 (.20–.50)	.47 (.26–.52)	.509
Onset-to-reperfusion time, min, median (IQR)	485 (321–734)	480 (330–725)	490 (310–758)	.948
mTICI score 2b-3, *n* (%)	297 (88.3)	143 (98.6)	154 (80.6)	<.001
Hemorrhagic transformation, *n* (%)	88 (26.1)	25 (17.2)	63 (32.9)	.001
Symptomatic intracranial haemorrhage, *n* (%)	35 (10.4)	4 (2.7)	31 (16.2)	<.001
NIHSS at 24 h, median (IQR)	10 (5–20)	5 (3–9)	18 (11–24)	<.001
Infarct volume at 24 h in mL, median (IQR)	26.4 (9.3–68.1)	16.9 (6–30)	44.1 (18.7–140.3)	.047

Abbreviations: ASPECTS, Alberta Stroke Programme Early CT Score; COVES, cortical vein opacification score; CVO, comprehensive venous outflow; EVT, endovascular treatment; ICA, internal cerebral artery; ICV, internal cerebral vein; IQR, interquartile range; MCA, middle cerebral artery; mRS, modified Rankin scale; mTICI, modified treatment in cerebral infarction; NCCT, noncontrast computed tomography; NIHSS, National Institutes Health Stroke Scale; PRECISE, prognostic evaluation based on cortical vein score difference in stroke; rCBF, relative cerebral blood flow; SD, standard deviation; Tmax, time-to-maximum; tPA, tissue plasminogen activator.



Statistic	PRECISE	COVES	CVO	ICV
Sensitivity (95% CI)	0.43 (0.39-0.46)	0.52 (0.46-0.58)	0.56 (0.51-0.62)	0.53 (0.45-0.60)
Specificity (95% CI)	0.56 (0.48-0.65)	0.64 (0.59-0.69)	0.69 (0.64-0.74)	0.61 (0.53-0.64)
Positive Predictive Value (95% CI)	0.72 (0.64-0.79)	0.55 (0.47-0.64)	0.64 (0.55-0.71)	0.42 (0.33-0.50)
Negative Predictive Value (95% CI)	0.27 (0.21-0.34)	0.61 (0.54-0.68)	0.62 (0.55-0.69)	0.71 (0.64-0.77)
Accuracy (95% CI)	0.47 (0.41-0.52)	0.59 (0.53-0.64)	0.63 (0.57-0.68)	0.59 (0.53-0.64)
	AUC difference (SE)		p	
CVO vs COVES	0.10 (0.04)		0.006	
CVO vs PRECISE	0.23 (0.04)		<0.001	
CVO vs ICV	0.14 (0.04)		<0.001	

FIGURE 2 PRECISE, COVES, CVO and ICV optimal values for recognizing AIS patients with good clinical outcomes as calculated using ROC curves. PRECISE indicates prognostic evaluation based on cortical vein score difference in stroke; AIS, acute ischemic stroke; COVES, cortical vein opacification score; CVO, comprehensive venous outflow; ICV, internal cerebral vein; ROC, receiver operating characteristic; SE, standard error. Outcome of interest: modified Rankin Scale 0 to 2 at 3 months.

4 | DISCUSSION

In this study, we performed a comparative analysis of different VO grading systems measured on mCTA to establish which of them had the best predictive ability for good clinical outcomes. We found that, although all VO scores were associated with favourable outcomes in the primary unadjusted analysis, after accounting for potential confounders, only CVO was an independent predictor of good outcome with an optimal cut-off value of ≥4. Our results confirmed the utility of VO as a prognostic biomarker in AIS patients undergoing EVT and remarked that a better evaluation of VO could be achieved when considering both superficial and deep venous structures. However, all these VO metrics showed moderate prognostic performance, with CVO demonstrating the greater discriminative ability for good functional outcomes. Therefore, these findings reinforce the added value of CVO assessment in association with other clinical and radiological parameters rather than supporting the use of CVO as a stand-alone measure for outcome prediction. Our study indicates that not all venous routes had the same impact in predicting good functional outcomes, suggesting that some with specific VO pathways could be structures more efficient than others in quantifying venous drainage of MCA territory. In particular, the superiority of CVO compared with PRECISE in predicting outcome seems to indicate that the vein of Trolard and the basal vein of Rosenthal, included in PRECISE but not in CVO, are not so relevant for superficial and deep VO from MCA territory, respectively. In fact, the anatomic variability of superficial venous flow affecting the veins of Trolard[26] could reduce the overall reliability in the evaluation of its cortical venous drainage. In addition, the infarcts of striato-capsular territory,

TABLE 3 Multivariable predictors of good functional outcome (mRS 0–2 at 3 months).

	OR (95% CI)	*p* Value
MODEL 1		
Age	1.02 (1.00–1.05)	.016
mRS before stroke	1.42 (1.10–1.83)	.007
Admission NIHSS	1.05 (1.01–1.10)	.003
Collaterals	1.99 (1.18–3.33)	.009
mTICI 2b-3	16.41 (3.51–74.69)	<.001
PRECISE score	.96 (.55–1.67)	.900
MODEL 2		
Age	1.02 (1.00–1.04)	.019
mRS before stroke	1.47 (1.13–1.91)	.003
Admission NIHSS	1.06 (1.02–1.10)	.004
Collaterals	1.82 (1.09–3.15)	.022
mTICI 2b-3	14.2 (3.12–64.93)	.001
COVES score	1.57 (.95–2.60)	.076
MODEL 3		
Age	1.02 (1.00–1.04)	.025
mRS before stroke	1.52 (1.17–1.99)	.002
Admission NIHSS	1.06 (1.02–1.10)	.004
Collaterals	1.69 (.99–2.91)	.054
mTICI 2b-3	13.19 (2.86–60.69)	.001
CVO score	2.51 (1.49–4.18)	.001
MODEL 4		
Age	1.03 (1.00–1.05)	.008
mRS before stroke	1.39 (1.08–1.81)	.011
Admission NIHSS	1.05 (1.01–1.10)	.008
Collaterals	.80 (.71–2.90)	.008
mTICI 2b-3	17.28 (3.77–79.19)	<.001
ICV score	.62 (.037–1.05)	.079

Note: Logistic regression with backward elimination at $p < .1$. Variables entered into the model: age, pre-stroke mRS, NIHSS, ASPECTS, mTICI, collateral score; venous outflow scores entered separately into different models.

Abbreviations: CI, confidence interval; COVES, cortical vein opacification score; CVO, comprehensive venous outflow; ICV, internal cerebral vein; mRS, modified Rankin scale; mTICI, modifiedtreatment in cerebral infarction; PRECISE, prognostic evaluation based on cortical vein score difference in stroke; NIHSS, National Institutes Health Stroke Scale; OR, odds ratio.

mostly drained by the basal vein of Rosenthal,[27] showed a limited impact on neurologic outcomes. Conversely, ICV, analysed only in CVO, drains the arterial vascular territories of the medial and lateral lenticulostriate arteries, the anterior choroidal arteries and the artery of Heubner demonstrating a more significant impact on clinical outcomes.[10] On the other hand, the lower prognostic ability of COVES with respect to the CVO could be attributed to the lack of analysis of deep venous circulation since a regular filling of ICV was associated with a lower infarct core growth, a reduced risk of hemorrhagic transformation and limited infarct edema.[14] Interestingly, in our study the evaluation of ICV asymmetry alone did not predict functional outcome, confirming the importance of assessing both superficial and deep venous networks in defining VO from MCA territory. However, this finding was in contrast with a recent report that did not show a significative difference between ICV asymmetry and CVO in identifying good functional outcome, but in a smaller population of patients and using sCTA.[28] Indeed, the assessment of these VO metrics with mCTA represents the main strength of our study as it is well-known that mCTA provides better temporal resolution and vascular enhancement than sCTA and, unlike sCTA, allows a precise evaluation of venous contrast filling in the peak venous phase that is considered the optimal time-point for the assessment of venous opacification.[3,8,27] Furthermore, a significant association between favourable CVO profiles and good arterial collaterals measured with both mCTA and HIR was found. As widely accepted, mCTA is the best rating tool for pial arterial (macrovascular) collaterals,[3] whereas HIR describes the amount of tissue-level (microvascular) collaterals.[29] The relationship between CTA pial arterial collaterals and favourable VO was also described by prior reports[7,11] but not confirmed by others.[18,30] This discrepancy might be explained by heterogeneity in the different venous structures selected for quantification of VO. However, the connection between tissue-level collaterals measured by HIR and good VO was in agreement with recent findings obtained with ICV[30] and COVES,[31] strengthening the importance of a combined evaluation of superficial and deep venous drainage. From a biological point of view, a favourable CVO might lead to better functional outcome allowing an optimal inflow and transit of blood, provided by arterial collaterals, through capillaries in ischemic tissue.[30,31] On the other hand, it has been demonstrated that venous engorgement could increase venous pressure, which impacts venules and capillaries, leading to rupture of blood brain barrier (BBB) and cerebral edema growth.[32] Therefore, our findings suggest that a favourable CVO profile could be associated with low BBB permeability, determinant of effective reperfusion, lower infarct growth and, consequently, better clinical outcomes after EVT.[33] Moreover, in line with previous evidence[14] we found that patients with higher CVO score achieved more frequently successful recanalization and had low rates of HT and symptomatic intracranial haemorrhage after EVT. Overall these findings further demonstrate the close relationship between a favourable CVO profile and BBB integrity. Impaired VO may also lead to capillaries endothelial dysfunction, resulting in the

TABLE 4 Clinical and neuroimaging features of patients with and without favourable CVO profile.

Variable	CVO favourable $n=164$	CVO unfavourable $n=172$	p $n=336$
Age, mean (±SD), years	73.9 (14.3)	76 (12.5)	.081
Admission NIHSS, median (IQR)	17 (10–21)	18 (12–23)	.004
mRS before stroke, median (IQR)	0 (0–2)	0 (0–2)	.131
ASPECTS, median (IQR)	8 (7–9)	7 (5–8)	.001
Good arterial collaterals, *n* (%)	116 (70.7)	83 (48.3)	<.001
Hypoperfusion intensity ratio, median (IQR)	.35 (.21–.52)	.47 (.24–.50)	.005
mTICI score 2b-3, *n* (%)	157 (95.7)	142 (82.5)	<.001
Hemorrhagic transformation, *n* (%)	38 (23.1)	50 (29.0)	.219
Symptomatic intracranial haemorrhage, *n* (%)	10 (6)	25 (14)	.020
mRS 0–2, *n* (%)	93 (54.0)	71 (43.3)	<.001
Mortality, *n* (%)	20 (12.1)	52 (30.2)	<.001
Infarct volume at 24 h in mL, median (IQR)	19.0 (6.0–38.1)	39.5 (16.5–130.3)	.084

Abbreviations: ASPECTS, Alberta Stroke Programme Early CT Score; CVO, comprehensive venous outflow; IQR, interquartile range; mRS, modified Rankin Scale; mTICI, modified treatment in cerebral infarction; NIHSS, National Institutes Health Stroke Scale; SD, standard deviation.

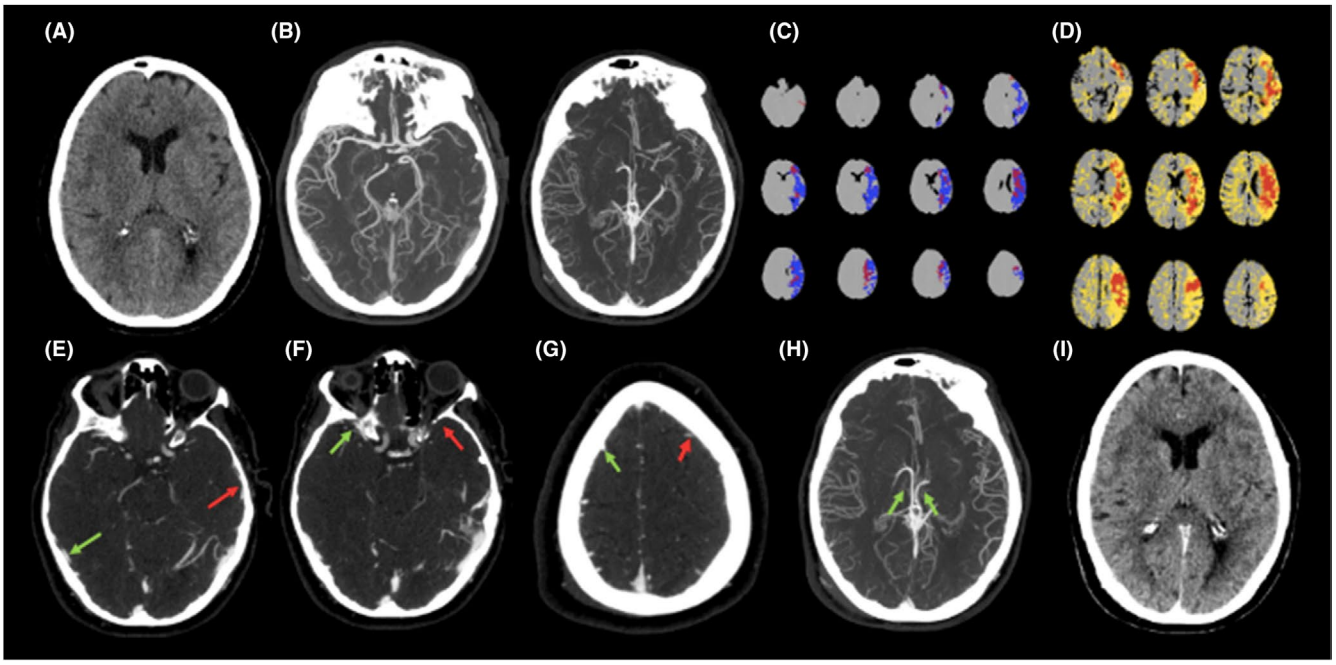


FIGURE 3 Illustrative case of comprehensive venous outflow (CVO) assessment in acute ischemic stroke (AIS) patient with occlusion of M1 segment of the left middle cerebral artery (MCA). A visible hypodensity on noncontrast computed tomography (NCCT) resulted in ASPECTS = 8 (involvement of I, M2 regions) (A), with good multiphase CT-angiography (mCTA) collaterals (Menon Score = 4) (B). CT-perfusion maps show a small core volume of 23 mL and extensive penumbra of 101 mL (C) with hypoperfusion intensity ratio of .34 (D). Red arrows indicate poor venous contrast opacification while green arrows point to cortical and deep veins with moderate or good contrast filling. Second phase of mCTA shows a less opacified vein of Labbé (E), an absent spheno-parietal sinus (F) and a less visible superficial medium cerebral vein (G) in the left hemisphere with respect to contralateral side resulting in cortical venous opacification score (COVES) of 2. The comparable opacification of internal cerebral vein between two sides indicates a CVO of 4 (H). Follow-up NCCT performed at 24 h reveals a small final infarct volume corresponding to the hypoattenuated NCCT lesion observed at admission without hemorrhagic transformation (I).

disruption of the BBB. Moreover, increased BBB permeability contributes to reperfusion injury and hemorrhagic complications after reperfusion therapies.[32] Future studies are needed to address the relationship between BBB permeability and CVO drainage pathways and patterns. Taken together, our results indicate that CVO seems to be an appealing parameter in addition to the evaluation of arterial input and microvascular collateral perfusion to identify subjects with overall good collateral status at multiple levels which could lead to a new and potentially automated assessment tool to improve clinical outcome in patients undergoing EVT. Future research is warranted to explore the reliability of this holistic approach in predicting good functional outcome in a real-world setting and establish whether the simultaneous assessment of deep and superficial venous structures could really represent an added value. Our study has some limitations. First, the small sample size collected at a single institution could reduce the consistency of our data. Second, as this study was based on a retrospective analysis, our findings require prospective validation. Third, we cannot exclude the influence of unmeasured confounders (deriving from patient comorbidities, such as atrial fibrillation or poor cardiac output in older patients, and their medical treatment, since all patients underwent EVT), which may influence VO assessment and introduce potential selection bias due to the nonrandomized design of our study. Fourth, venous opacification has been reported to be affected by the selected imaging protocol, including acquisition timing and rate of contrast injection.[18] Therefore, prospective studies are needed to determine optimal CVO thresholds for EVT selection and outcome prediction in AIS patients with LVO and improve the generalizability of our results. Thus, a replication cohort is needed to test the reliability of CVO in different clinical population before considering the inclusion of the CVO into EVT triage protocol. Finally, multiple-center studies with larger sample sizes are warranted to provide further confirmation of our results.

5 | CONCLUSIONS

Our study demonstrated that CVO score assessed by mCTA was the most reliable grading system for determining VO and predicting clinical outcome in AIS patients receiving EVT. Future studies are warranted to test CVO across different clinical populations, not only for predicting functional outcomes but also other critical endpoints such as hemorrhagic transformation, infarct growth and malignant cerebral edema. Moreover, integrating CVO with other prognostic markers, such as arterial inflow and microperfusion collaterals, might lead to a deeper and more granular assessment of collateral networks' biology.

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DATA AVAILABILITY STATEMENT

The complete dataset used for this study will be shared on request from any qualified researcher to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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