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Connecting the DOTs: a novel imaging sign on flat-panel detector CT indicating distal vessel occlusions after thrombectomy

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ABSTRACT

Background Immediate non-contrast post-interventional flat-panel detector CT (FPDCT) has been suggested as an imaging tool to assess complications after endovascular therapy (EVT). We systematically investigated a new imaging finding of focal hyperdensities correlating with remaining distal vessel occlusion after EVT.

Methods A single-center retrospective analysis was conducted for all acute ischemic stroke patients admitted between July 2020 and December 2022 who underwent EVT and immediate post-interventional FPDCT. A blinded core lab performed reperfusion grading on post-interventional digital subtraction angiography (DSA) images and evaluated focal hyperdensities on FPDCT (here called the distal occlusion tracker (DOT) sign). DOT sign was defined as a tubular or punctiform, vessel confined, hyperdense signal within the initial occlusion target territory. We assessed sensitivity and specificity of the DOT sign when compared with DSA findings.

Results The median age of the cohort (n=215) was 74 years (IQR 63–82) and 58.6% were male. The DOT sign was positive in half of the cohort (51%, 110/215). The DOT sign had high specificity (85%, 95% CI 72% to 93%), but only moderate sensitivity (63%, 95% CI 55% to 70%) for detection of residual vessel occlusions. In comparison to the core lab, operators overestimated complete reperfusion in a quarter of the entire cohort (25%, 53/215). In more than half of these cases (53%, 28/53) there was a positive DOT sign, which could have mitigated this overestimation.

Conclusion The DOT sign appears to be a frequent finding on immediate post-interventional FPDCT. It correlates strongly with incomplete reperfusion and indicates residual distal vessel occlusions. In the future, it may be used to complement grading of reperfusion success and may help mitigating overestimation of reperfusion in the acute setting.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Focal vascular hyperdensities on flat-panel detector CT (FPDCT) performed immediately after endovascular therapy have been suggested to indicate residual thrombi, but no systematic investigations are available.

WHAT THIS STUDY ADDS

⇒ Focal vascular hyperdensities on immediate post-interventional FPDCT—the DOT (distal occlusion tracker) sign—are easily identifiable and correlate strongly with final reperfusion success, thus indicating residual vessel occlusions. Reviewing FPDCT for the DOT sign can mitigate Thrombolysis In Cerebral Infarction (TICI) overestimations in half of patients falsely graded as completely reperfused (TICI 3) by the operators.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The DOT sign may be used to complement grading of reperfusion success and helps to mitigate overestimation of reperfusion in the acute setting.

INTRODUCTION

Endovascular treatment (EVT) for acute ischemic stroke patients is continuously evolving with new generation of devices and an expanding list of eligibility criteria.[1] Despite these advances, not all patients achieve complete reperfusion, defined as an expanded Thrombolysis In Cerebral Infarction score 3 (eTICI 3).[2 3] Several adjunctive reperfusion strategies have been proposed once incomplete reperfusion (eTICI <3) is encountered at the end of an intervention; however, the safety profile of these reperfusion efforts is not completely understood.[4–6] Moreover, it is unclear which stroke patient subgroups might be more likely to benefit from these additional reperfusion efforts, where the risk-benefit ratio is lower.[7–9]

The present reference standard for evaluating reperfusion success is on two-dimensional digital subtraction angiography (DSA) imaging which is acquired at the end of the intervention. Despite DSA being the reference standard, it has limitations such as overprojection of territories and vessels.[10] This might lead to overestimation of reperfusion success by the treating interventionalist, especially

in the acute setting and when estimating reperfusion success in subtle distal territories or areas of overlapping capillary phase hypoperfusion.[11]

Recently, a case series suggested focal vascular hyperdensities on flat-panel detector CT (FPDCT) as an imaging correlate of remaining distal vessel occlusions after EVT.[12] Contrast staining of fragmented thrombi or contrast stagnation proximal to the clot have been proposed as pathophysiological explanations.[12] A systematic evaluation of this imaging finding, however, was never performed. We aimed to assess the prevalence of focal vascular hyperdensities, together with its association to baseline characteristics and reperfusion success. Moreover, we evaluated the sensitivity and specificity of the finding to detect residual vessel occlusions and its potential to mitigate overestimation of reperfusion success by operators in the acute setting.

METHODS

Patient population

A single-center retrospective analysis was performed from a prospective registry of all consecutively admitted acute ischemic stroke patients from July 2020 until December 2022. All patients who underwent EVT and immediate post-interventional FPDCT were assessed for eligibility. The local ethics committee approved this study, all patients gave informed consent for taking part and all study protocols were implemented according to the Declaration of Helsinki. Study data are available from the corresponding author upon request and after ethics committee clearance. The present study has been reported according to the Standards for Reporting Diagnostic Accuracy (STARD) statement for diagnostic studies.

FPDCT image acquisition

Details on FPDCT acquisition have been described previously.[13] In short, FPDCT was acquired using a biplane flat-panel detector angiographic system (ARTIS Icono and Artis Q, Siemens Healthineers AG, Forchheim, Germany). Conventional protocol (20sDCT head) uses a planar rotation over 200° with an angular increment of 0.4°, adding up to 496 projection images. The craniocaudal angle stayed at zero, while the scan was performed from right anterior oblique (RAO) 100 to left anterior oblique (LAO) 100. A new protocol (syngo DynaCT Sine Spin) offers a craniocaudal modulation in sense of a sine curve: scan over 220° from RAO 110 to LAO 110 with an amplitude of 10°. Scanning starts at −110°/0°, goes through −55°/10°, 0°/0° and 55°/−10°, finishing at 110°/0°. With an angular increment (0.4°), this adds up to 546 projections. The new protocol can be used as 7sDCT Sine Spin (4×4 binning and a soft reconstruction), that can visualize soft tissue changes (eg, hemorrhage or infarcted tissue). Only patients with available 1 mm slice thickness reconstructions of the FPDCT were considered for review. At the study beginning, the decision on performing FPDCT was at the discretion of an interventionalist. FPDCT was more likely to be performed in the following scenarios: complex interventions (multiple maneuvers, distal thrombectomies, need for antiplatelets in emergency stenting), tandem occlusions, intracranial stenosis, peri-interventional dissection in the cervical vessel; potential administration of adjunctive intra-arterial lytics; ruling out hemorrhages or other potential complications (see 'Neuroimaging evaluation' below). However, after the initial study period, all institutional operators acquired FPDCT systematically after every acute stroke intervention.

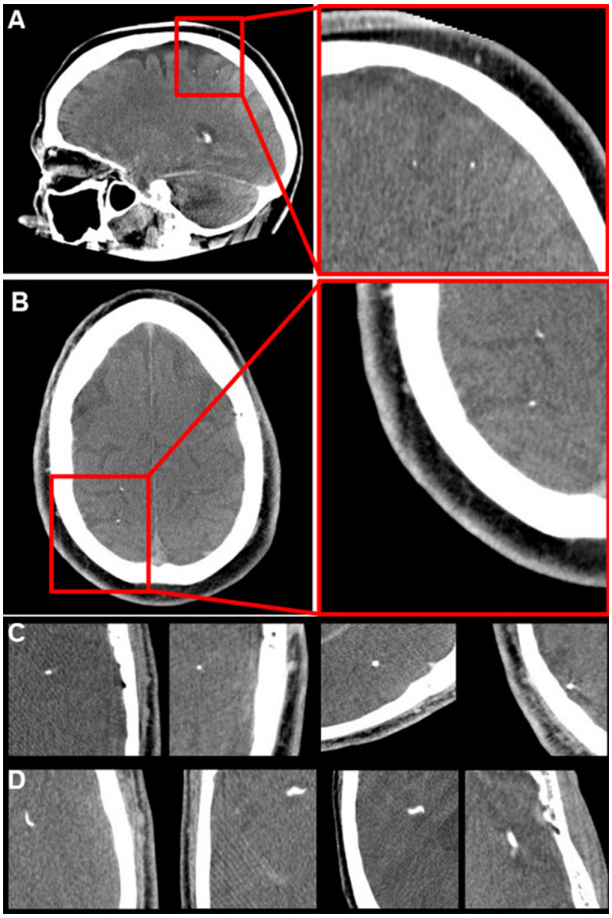

Figure 1 DOT sign variations. Female patient with an M1-MCA occlusion who was graded as TICI 3 by the operator in the acute interventional report and eTICI 2c by the core lab. (A, B) Sagittal and axial plane of the immediate post-interventional cross-sectional FPDCT shows two positive DOT signs, suggestive of residual vessel occlusions. (C, D) Different examples of a positive DOT sign as punctiform (C) or tubular (D) hyperdense signal increase in the course of an intracranial artery within the initial target territory of the endovascular therapy. DOT, distal occlusion tracker; eTICI, expanded Thrombolysis In Cerebral Infarction; FPDCT, flat-panel detector CT; MCA, middle cerebral artery.

Neuroimaging evaluation

Identification of the vessel occlusion site and collateral grading was performed on the baseline DSA run. Reperfusion was graded on the final antero-posterior and lateral whole brain DSA runs by a core lab using the eTICI scale. For the sensitivity analysis, we also report operator-graded TICI scores. Operator grading was performed by the treating interventionalist at the end of the procedure and was extracted from the acute interventional report, which was written immediately after the intervention. Throughout the manuscript, eTICI refers to the core lab assessed reperfusion success, while $TICI^{OP}$ refers to the operator assessed reperfusion success. For $TICI^{OP}$ no distinction between TICI 2b50 and TICI 2b67 was available.

The distal occlusion tracker (DOT) sign was evaluated on the FPDCT, which was acquired immediately after the intervention while the patient was on the angiography table. The DOT sign was rated as present if there was a punctiform or tubular hyperdense signal increase in the course of an intracranial artery within the initial EVT target territory (figures 1–2). Conversely, the DOT sign was rated as absent in case no punctiform or tubular hyperdense signal increase could be seen within the

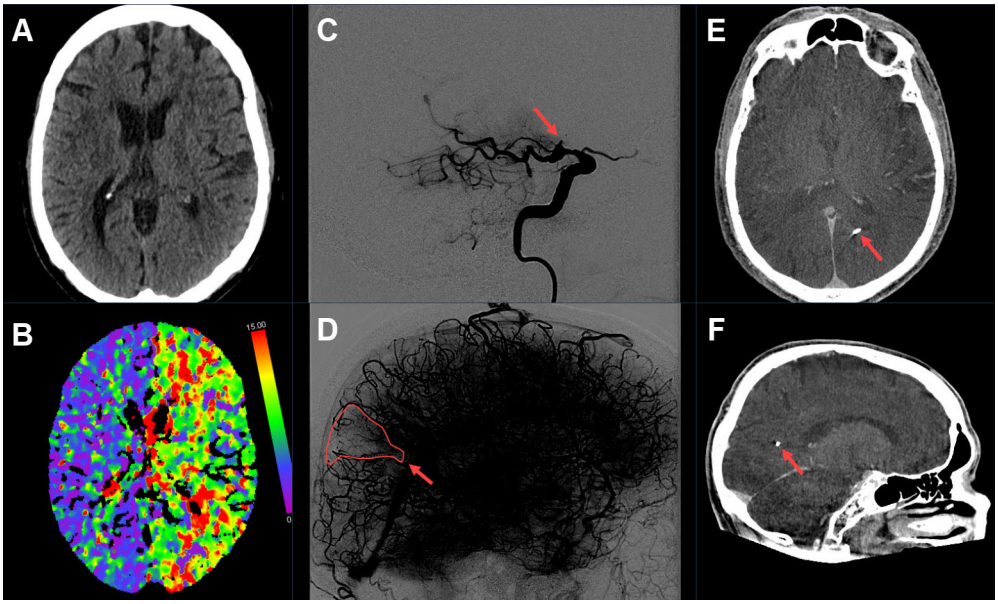

Figure 2 Positive DOT sign with incomplete reperfusion. (A, B) Admission imaging shows hypoperfusion (TTP map) corresponding to a left-side ICA occlusion. (C) First angiography run confirms occlusion location in the left ICA (red arrow). (D) Final angiography imaging shows almost complete reperfusion (eTICI 2c, non-perfused area bordered in red) with a residual distal occlusion (red arrow). (E) Immediate post-interventional cross-sectional FPDCT shows a positive DOT sign which directly corresponds to the position of the residual vessel occlusion (red arrow). (F) Sagittal projection of the FPDCT imaging reveals the same finding with a positive DOT sign. DOT, distal occlusion tracker; eTICI, expanded Thrombolysis In Cerebral Infarction; FPDCT, flat-panel detector CT; ICA, internal carotid artery; TTP, time to peak.

target territory (online supplemental figure S1). This definition and findings from regular follow-up imaging were used to differentiate between the DOT sign and other hyperdense findings on FPDCT, such as subarachnoid extravasation of contrast and cellular blood elements/subarachnoid hyperdensities (online supplemental figure S2 and respective caption for Methodology and online supplemental figure S3 and respective caption for Methodology), parenchymal contrast extravasation and hemorrhage (online supplemental figure S4 and respective caption for Methodology) or intracranial calcifications.[14–16] In case there was more than one positive DOT sign on FPDCT, the number of DOT signs was noted. For the per-vessel analysis, the DOT sign from the FPDCT imaging was spatially correlated to the corresponding location on the final DSA runs. Only cases where all the DOT signs could be directly superposed on the final DSA run were evaluated as concordant (online supplemental figure S5). Reperfusion grading (eTICI) and DOT sign evaluation were performed by an independent core lab, blinded to technical and clinical details (years of neuroradiology training: >15, >10, >4, >3 and >1 year). The core lab was blinded to DSA findings for FPDCT evaluation and vice-versa.

Variables and statistical analysis

Baseline imaging was used to categorize occlusion site location into one of the following: internal carotid artery (ICA), proximal segment of the middle cerebral artery (M1), insular segment of the middle cerebral artery (M2), opercular segment of the middle cerebral artery (M3), pre-communicating and post-communicating segment of the anterior cerebral artery (A1–2) or posterior circulation occlusion. The American Society of Intervention and Therapeutic Neuroradiology and the Society of Interventional Radiology (ASITN/SIR) scale was used for collateral grading which was done on the initial DSA series. The grading system ranges from 0 to 4: 0=no visible collaterals; 4=rapid blood flow in the ischemic area. Total contrast amount for the entire intervention (DSA+FPDCT) was extracted from the acute interventional report. DSA-FPDCT time refers to the period between the final intracranial DSA run and FPDCT imaging. Overestimation in the final reperfusion score was present if the operator graded the case as complete reperfusion ($TICI^{OP}$=3) and the core lab graded the case as incomplete reperfusion (eTICI <3). Clinical outcomes were evaluated with the National Institutes of Health Stroke Scale (NIHSS) at 24 hours and modified Rankin scale (mRS) score at 3 months after the intervention. Strong neurological improvement (denoted in the text as "c-NIHSS") was defined as either the difference between NIHSS at 24h and admission ≥8 points or NIHSS at 24h ≤1.[17] Early neurological deterioration was defined as an increase in the NIHSS score by ≥4 points between admission and 24h. Functional independence was defined as the mRS score 0–2 at 3 months.

Results are reported as either n (%) or median (IQR). The Fisher's exact and Mann-Whitney U tests are used for categorical and continuous variables, respectively. Inter-rater agreement for the presence of the DOT sign is reported with Krippendorff's α coefficient. Frequency between the DOT sign and eTICI score is presented in a contingency table and the χ^2 test was used to determine the association between the two. The ability of the DOT sign to detect residual vessel occlusion (dichotomized: present/absent) was calculated by comparing it to the core lab's grading of complete reperfusion (dichotomized: eTICI=3/eTICI <3). The diagnostic performance of the DOT sign is reported with sensitivity, specificity, and accuracy. For the per-vessel analysis, the number of DOTS and the number of residually occluded vessels was dichotomized (one/more than one) and the results are reported in the form of a contingency matrix. To assess and account for a potential selection bias we compared patients who did and did not receive FPDCT. We excluded all FPDCT patients where additional maneuvers were performed after acquisition of the FPDCT or interventional material was

still in place intracranially (see Methods). All statistical analyses were conducted using R v4.0.0.

RESULTS

During the study period 525 patients underwent EVT, of whom 259 had undergone FPDCT. Out of these 259 screened patients, 215 patients were included in the final analysis (online supplemental figure S6). Exclusion criteria during the screening period were: FPDCT was not acquired at the end of an intervention, 1 mm slice thickness reconstructions from the FPDCT were not available, there was intracranial placement of a microcatheter or other material, and FPDCT was performed as perfusion imaging and not as non-contrast CT. Inter-rater agreement for DOT sign evaluation was very good (Krippendorff's α 0.90, 95% CI 0.87 to 0.92). The median age of the final cohort was 74 years (IQR 63–82), 58.6% were male, and the median admission NIHSS score was 10 (IQR 5–18). About half of the entire cohort showed a positive DOT sign (51%, 110/215) on FPDCT. When compared to patients with the negative DOT sign, patients who had a positive DOT sign had lower rates of hyperlipidemia at admission (69.5% vs 53.6%, P=0.02), fewer posterior circulation strokes (15.2% vs 7.5%, P=0.03), and shorter median DSA-FPDCT time (4 min(3–10) vs 4 min(3–7), P=0.04). Other baseline and interventional characteristics were comparable between the groups (table 1 and online supplemental table S1).

During the study period, patients with available FPDCT tended to have more large-artery strokes and lower rates of complete reperfusion when compared with the patients in whom no FPDCT was accquired (eTICI 3: 25% vs 38%, P=0.003) (online supplemental table S2).

There was a strong association between the final eTICI score and a positive DOT sign—that is, patients on the lower spectrum of the eTICI scale were more likely to have a positive DOT sign (eTICI <3: 63.0% vs eTICI 3: 15.1%, P<0.001) (online supplemental figure S7). Moreover, the number of positive DOTs was also strongly correlated with the final reperfusion grade and this was evident across the entire eTICI scale (eg, eTICI 2a vs eTICI 2c: 1 (0–3) vs 1 (0–2), P<0.001) (online supplemental table S3). Comparable results were shown when comparing the $TICI^{OP}$ and the DOT sign (online supplemental table S4).

The DOT sign had high specificity (85%, 95% CI 72% to 93%), moderate sensitivity (63%, 95% CI 55% to 70%), and accuracy (68%, 95% CI 62% to 75%) in detection of residual vessel occlusions when compared with the core lab adjudicated reperfusion grading (online supplemental table S5). For the per-vessel analysis, FPDCT enabled detection of additional occlusions in 64% of cases (68/107) (online supplemental table S6) when compared to ratings based on the final DSA runs alone.

The operators (in comparison to core lab) overestimated $TICI^{OP}$ 3 in 25% (53/215) of cases. In more than half of these cases (53%; 28/53 patients) there was a positive DOT sign, which could have mitigated this overestimation. There were 14 cases with eTICI 3 ratings by the core lab with a positive DOT sign. Re-evaluation of the images changed the final reperfusion grading in 7/14 cases, with seven of these patients now rated as <eTICI 3.

Compared to patients with a negative DOT sign, those with a positive DOT sign had lower rates of strong neurological improvement (45.7% vs 23.9%, P<0.001) (online supplemental figure S8) and functional independence (69.3% vs 50.0%, P=0.008) (online supplemental figure S9). Difference in these outcomes was present across all eTICI scores (online supplemental figure S10). Moreover, patients with a positive DOT sign were more likely to have early neurological deterioration (21.1% vs 9.5%, P=0.03). In the multivariate regression analysis for mRS 0–2, both the DOT sign and the eTICI score showed strong association with functional independence at 3 months (online supplemental table S7).

DISCUSSION

This study demonstrates the following: (1) The DOT sign is an easily identifiable imaging finding on immediate post-interventional FPDCT and is present in about half of patients undergoing EVT. (2) The DOT sign correlates strongly with the final reperfusion score and indicates residual vessel occlusions. (3) The DOT sign is highly specific (ie, if the DOT sign is positive, an occlusion is likely present), but not very sensitive for the detection of remaining vessel occlusion. (4) Reviewing FPDCT for the DOT sign can mitigate TICI overestimations, as half of the patients falsely graded as complete reperfusion (TICI 3) by the operator showed a positive DOT sign. (5) The DOT sign may be an additional parameter to assess clot fragmentation of devices or thrombectomy techniques.

DOT sign on FPDCT

The presence of a punctiform hyperdense signal on immediate post-interventional FPDCT has been described previously.[12] In a small retrospective series (n=49), eight patients showed punctiform hyperdense signal increase on FPDCT performed immediately after EVT. The authors defined this as iodine-stained fragmented thromboembolism (ISFT), hypothesizing that the most likely explanation for their findings is a penetration of contrast into the distal thromboembolism that had occurred during the intervention, or represents stasis of residual contrast proximal to the thromboemboli.[12] In the present study, we have defined the DOT sign as a punctiform or tubular hyperdense signal in the course of an intracranial artery in the target territory. We also found the DOT sign to be frequent, being present in half of the entire cohort. The most likely reasons for the difference in prevalence between these two studies seem to be: study design (retrospective cohort vs case series), reading process (independent core lab vs two neuroradiologists), study period with improved imaging quality on new generation angiography systems (2022 vs 2016), FPDCT slice thickness (1 vs 3 mm), and operational definitions of the post-interventional FPDCT findings (DOT sign: punctiform or tubular hyperdense signal increase in the course of an intracranial artery within the initial EVT target territory vs ISFT: luminal filling defect with greater Hounsfield density compared with the contralateral side).[12] The exact pathophysiological explanation for the DOT sign remains unclear and needs to be investigated in further studies. Both contrast stagnation proximal to the occlusion and penetration of contrast material into the thrombus need to be considered.[18–20] Multiple studies have shown that thrombus density increases after administration of intravenous contrast. However, densities of thrombi in acute ischemic stroke patients rarely exceed 200 Hounsfield units, which is well below the value observed on FPDCT in our cohort.[18] Still, and considering intra-arterial injection of contrast, the phenomenon of thrombus perviousness could partially explain hyperdense foci found along the vessel course, and heterogeneity regarding its prevalence may be attributed to differences in thrombus histology.[19 20] On the other hand, high-pressure injection with a large bore catheter during a diagnostic run may replace stagnating blood proximal to the thrombus. Due to anatomical factors and a lack of high enough pressure, a column of highly concentrated contrast may then stagnate proximal to the clot (see figure 3A–B and next paragraph).

Table 1 Patient baseline and interventional characteristics

		Overall	Negative DOT sign	Positive DOT sign	P value
n		215	105	110	
Baseline					
Age, years (median (IQR))		74 (63–82)	73 (63–81)	75 (64–82)	0.246
Sex, male (%)		126 (58.6)	64 (61.0)	62 (56.4)	0.586
Atrial fibrillation, yes (%)		67 (31.2)	31 (29.5)	36 (32.7)	0.719
Coronary heart disease, yes (%)		32 (14.9)	15 (14.3)	17 (15.5)	0.961
Diabetes, yes (%)		48 (22.3)	22 (21.0)	26 (23.6)	0.758
Hyperlipidemia, yes (%)		132 (61.4)	73 (69.5)	59 (53.6)	0.024
Hypertension, yes (%)		157 (73.0)	81 (77.1)	76 (69.1)	0.240
Smoking, yes (%)		56 (26.0)	29 (27.6)	27 (24.5)	0.720
Anticoagulants pre-stroke, yes (%)		20 (9.3)	9 (8.6)	11 (10.0)	0.900
Antiplatelets pre-stroke, yes (%)		42 (19.5)	20 (19.0)	22 (20.0)	0.997
NIHSS on admission (median (IQR))*		10 (5–18)	10 (4–18)	11 (5–17)	0.633
Onset-to-door (min) (median (IQR))*		169 (95–518)	166 (93–436)	180 (100–548)	0.736
Occlusion site (%)†	ICA	43 (21.0)	16 (16.2)	27 (25.5)	0.027
	M1	63 (30.7)	36 (36.4)	27 (25.5)	
	M2	64 (31.2)	28 (28.3)	36 (34.0)	
	M3	10 (4.9)	2 (2.0)	8 (7.5)	
	A1-2	2 (1.0)	2 (2.0)	0 (0.0)	
	Posterior	23 (11.2)	15 (15.2)	8 (7.5)	
Intervention					
Intravenous thrombolysis, yes (%)‡		94 (44.1)	43 (41.7)	51 (46.4)	0.589
Maneuver count (median (IQR))		2 (1–3)	2 (1–3)	2 (1–3)	0.062
eTICI (%)	0	5 (2.3)	3 (2.8)	2 (1.8)	<0.001
	1	2 (0.9)	0 (0.0)	2 (1.8)	
	2a	11 (5.1)	4 (3.8)	7 (6.4)	
	2b50	30 (14.0)	8 (7.6)	22 (20.0)	
	2b67	46 (21.4)	16 (15.2)	30 (27.3)	
	2c	68 (31.6)	29 (27.6)	39 (35.5)	
	3	53 (24.7)	45 (42.9)	8 (7.3)	
Guiding catheter (%)	No balloon	85 (39.5)	45 (42.9)	40 (36.4)	0.404
	Balloon	130 (60.5)	60 (57.1)	70 (63.6)	
Contrast dose (mL, median (IQR))		140 (100–190)	140 (100–186)	150 (100–200)	0.379
DSA-FPDCT time (min) (median (IQR))		4 (3–7)	4 (3–10)	4 (3–7)	0.044
Outcome					
c-NIHSS*		74 (34.6)	48 (45.7)	26 (23.9)	0.001
Early neurological deterioration*		33 (15.4)	10 (9.5)	23 (21.1)	0.031
mRS 0–2 at 90 days§		126 (59.5)	72 (69.3)	54 (50.0)	0.008

*Data missing for 1 patient.
†Data missing for 10 patients.
‡Data missing for 2 patients.
§Data missing for 3 patients.
DOT, distal occlusion tracker; DSA, digital subtraction angiography; eTICI, extended Thrombolysis In Cerebral Infarction; FPDCT, flat-panel detector CT; ICA, internal carotid artery; NIHSS, National Institutes of Health Stroke Scale.

DOT sign in detection of incomplete reperfusion

Interestingly, we found nearly half of the <eTICI 3 cases to have a negative DOT sign, which indicates that vessel occlusions are present without contrast accumulating before or within the thrombus. One potential reason for <eTICI 3 DOT negative cases is that the contrast stagnating proximal to the thrombus is washed out within the interval between the last angiography series and acquisition of FPDCT. This is supported by the observation that the delay between the last angiography and FPDCT was slightly longer in patients with a negative DOT sign. Still, this heterogeneity alone is insufficient to explain this discrepancy. We hypothesize that anatomical factors and the exact location of the persisting vessel occlusion may strongly influence the occurrence of the DOT sign. If the residual thrombus is logged

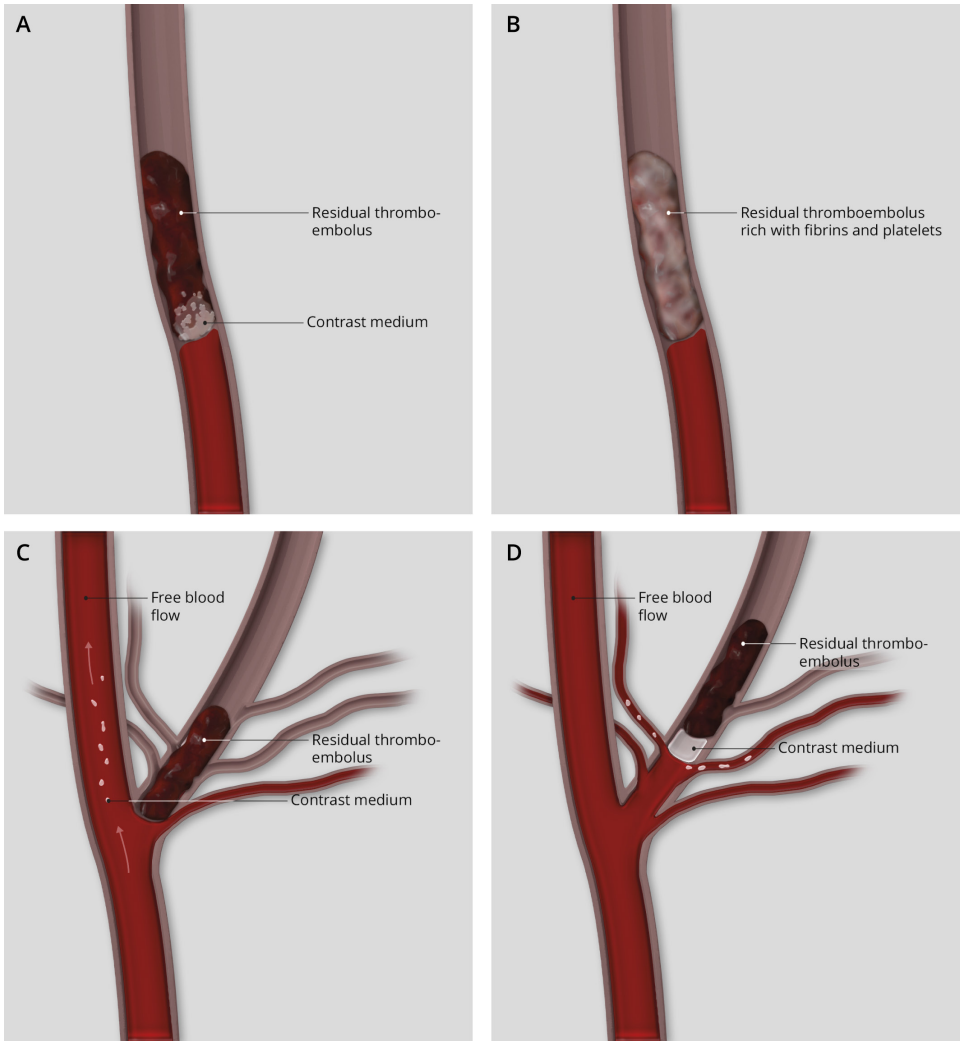

Figure 3 DOT sign and thrombus. The exact pathophysiological explanation for the DOT sign is currently unclear. Here we propose a few theoretical scenarios. (A) Parts of the contrast medium are diffusing through the proximal part of the residual thromboembolus which is rich with erythrocytes. (B) Residual thrombus consits mostly of fibrins and platelets, making it more difficult for the contrast to diffuse into the thrombus. (C) Residual thromboembolus is positioned directly at the blood vessel bifurcation. Any potential contrast medium is carried away by the blood flow leading to a complete contrast washout. This could result in a lack of hyperdense signal increase on the FPDCT (ie, negative DOT sign) despite the presence of a residual thromboembolus. (D) Residual thromboembolus is positioned just distal to a vessel bifurcation and contrast medium has stagnated proximal to the thrombus. Multiple secondary vessel bifurcations may lead to the washout of the leftover contrast. This would again result in a lack of a hyperdense signal increase on the FPDCT (ie, negative DOT sign), despite present residual thromboembolus. DOT, distal occlusion tracker; FPDCT, flat-panel detector CT.

in a vessel bifurcation, blood can still freely flow in the non-occluded branch (figure 3C–D). This could lead to the washout of the residual contrast proximal to the remaining thrombus and lead to the lack of hyperdense signal increase on the FPDCT (ie, negative DOT sign) despite a thrombus being present. Another explanation noted during the training and rating process was that the DOT sign can easily be overlooked when the vessel occlusion is in close proximity to the skull (online supplemental figure S11). An iodine-like density on FPDCT can easily be mistaken as part of the skull periosteum. Difference in Hounsfield units, windowing, and comparison to the admission CT could, in our experience, mitigate these false negative DOT sign ratings.

Notably, the DOT sign was positive in 14% (7/49) of cases where the blinded core lab rated reperfusion to be eTICI 3. However, with the knowledge of the DOT sign location, eTICI 3 grading was revised in some, but not all, of the cases. Potential explanations for false positive ratings may include subarachnoid, falcine or parenchymal calcifications and small subarachnoid or parenchymal contrast agent extravasations.

DOT sign in patient management and technique evaluation

Post-interventional FPDCT immediately after EVT can provide clinically relevant information. This entails contrast extravasation or hemorrhage after mechanical maneuvers, as well as early assessment of irreversible infarcted brain tissue at risk for hemorrhagic transformation, evident by parenchymal hyperdensities.[14–16] Here, we report another clinically applicable imaging sign of immediate post-interventional FPDCT.

Incomplete reperfusion is seen in more than half of all EVT-treated acute ischemic stroke patients and remains a notable concern, limiting the benefit of EVT.[2 3] The DOT sign could compliment the decision-making process in the angiography suite and advise potential adjuvant treatment options (eg, secondary mechanical thrombectomy or intra-arterial lytics).

Presently there is no level A evidence on the safety and efficacy of these rescue treatment options; therefore, the DOT sign could facilitate optimal benefit and minimize potentially harmful effects of these adjuvant treatments.[4–6] This is further supported by an association between the DOT sign and clinical outcomes. Patients with a positive DOT sign were more likely to have poorer outcome with early clinical deterioration and could represent a cohort of patients more likely to benefit from adjuvant reperfusion efforts.

There is a growing body of evidence that overestimation of reperfusion by the operators is high, and related to certain factors such as anatomical location of the residual occlusion and off-hours assessment.[10 11] In this analysis, we found a strong correlation between the final reperfusion score and the DOT sign across the entire eTICI scale. Importantly, the DOT sign was very specific, which means that if seen, the likelihood of a complete reperfusion is very low. In an emulated real-life scenario, recognizing the positive DOT sign could have mitigated false eTICI 3 ratings in half of the cases. Lastly, the DOT sign helps to assess eloquence of the remaining hypoperfused territory because a three-dimensional (3D) location of the clot is now possible.[13] Although the exact delineation of the hypoperfused territory cannot be discerned from the position of the clot, a combination of the projection of the capillary phase deficit of the clot and the 3D location of the occlusion can help in assessing eloquence in a more sophisticated manner.

Lastly, the DOT sign may be a useful adjunct in the comparison of thrombectomy techniques in the future. More and more devices are entering the market, but the rates of first-pass reperfusion and overall reperfusion success stay relatively similar. The occurrence and number of DOTs may provide additional information regarding the likelihood of fragmentation, but also the number of fragments. In addition, we postulate that automated detection of the DOT sign is easier than complex automatization of TICI scores,[21 22] further strengthening its potential value in clinical routine - especially when native CT scans before thrombectomy are available. We think that it should be relatively straightforward to develop algorithms which categorize and segment vessel-confined DOT signs.

Limitations

This is a single-center observational retrospective study accompanied by study-design related biases. First, patients did not undergo FPDCT within a prospective trial, but at the discretion of the treating physician. Patients who underwent FPDCT tended to have lower rates of complete reperfusion; hence the absolute rates of DOT sign positive patients may be lower in an unselected population. Moreover, patient movement may limit the interpretation from FPDCT. Second, all the FPDCT scans were acquired with a Siemens machine, limiting the generalizability of our results to other FPDCTs. Third, the exact pathophysiological correlate of the DOT sign could not be deduced from our analysis and we did not evaluate the histological composition of the thrombi potentially influencing its occurrence. Fourth, decreasing overestimation of complete reperfusion by operators appears useful, but the clinical benefit of reducing these rates is not proven. During the study period, the first-line technique was combined stent retriever and distal aspiration; therefore, it remains unclear if the DOT sign incidence would differ based on other first-line techniques. Due to everything stated above, we advise caution when correlating the DOT sign with clinical outcomes. Future studies should explore the clinical implications of the DOT sign and its usefulness in the decision-making process of pursuing additional reperfusion attempts once incomplete reperfusion has been observed.

CONCLUSION

The DOT sign is a frequent finding on immediate post-interventional FPDCT. It correlates strongly with incomplete reperfusion and helps to identify residual distal vessel occlusions. It may be used to complement grading of reperfusion success and may help to mitigate overestimation of reperfusion in the acute setting.

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SUPPLEMENT MATERIAL

Connecting the DOTs: A novel imaging sign on flat-panel detector CT indicating distal vessel occlusions after thrombectomy

Table of Contents

Table S1 Patient Baseline Characteristics

		Overall	Negative DOT sign	Positive DOT sign	p
n		215	105	110	
BASELINE					
Systolic blood pressure (median [IQR])*		156 [135, 175]	158 [137, 179]	155 [133, 170]	0.322
Diastolic blood pressure (median [IQR])*		83 [69, 95]	81 [70, 96]	84 [68, 95]	0.895
Creatinine (median [IQR])		80 [67, 95]	81 [68, 96]	80 [67, 94]	0.793
Glucose on admission (mmol/L) (median [IQR])†		7 [6, 8.4]	7.2 [6.1, 8.4]	6.9 [5.8, 8.5]	0.536
Time of symptom onset known (%)	No	35 (16.3)	13 (12.4)	22 (20.0)	0.237
	Wake up	37 (17.2)	21 (20.0)	16 (14.5)	
	Yes	143 (66.5)	71 (67.6)	72 (65.5)	
Etiology (%)‡	Cardiac embolism	67 (32.4)	39 (38.2)	28 (26.7)	0.194
	Cervical artery dissection	8 (3.9)	3 (2.9)	5 (4.8)	
	Large artery atherosclerosis	48 (23.2)	26 (25.5)	22 (21.0)	
	More than one possible etiology	8 (3.9)	5 (4.9)	3 (2.9)	
	Other determined etiology	6 (2.9)	1 (1.0)	5 (4.8)	
	Patent foramen ovale	2 (1.0)	1 (1.0)	1 (1.0)	
	Unknown etiology	68 (32.9)	27 (26.5)	41 (39.0)	

*Data missing for one patient. †Data missing for two patients.

Table S2 Baseline and Intervention Characteristics of Comparator and Study Group

		Overall	Comparator group (EVT only)	Study group (EVT + FPDCT)	p	Missing (%)
n		481	266	215		
BASELINE						
Age (median [IQR])		76 [65, 83]	76 [66, 85]	75 [65, 82]	0.221	0.4
Sex = Male (%)		265 (55.3)	139 (52.7)	126 (58.6)	0.226	0.4
Atrial fibrillation = Yes (%)		161 (34.4)	94 (37.2)	67 (31.2)	0.207	2.7
Coronary heart disease = Yes (%)		80 (17.1)	48 (19.0)	32 (14.9)	0.286	2.9
Diabetes = Yes (%)		93 (19.9)	45 (17.9)	48 (22.3)	0.276	2.9
Hyperlipidemia = Yes (%)		281 (60.2)	149 (59.1)	132 (61.4)	0.686	2.9
Hypertension = Yes (%)		336 (71.9)	179 (71.0)	157 (73.0)	0.708	2.9
Smoking = Yes (%)		120 (25.4)	64 (24.8)	56 (26.0)	0.839	1.7
Systolic blood pressure (median [IQR])		157 [137, 175]	158 [140, 175]	156 [135, 175]	0.669	0.8
Diastolic blood pressure (median [IQR])		81 [68, 96]	81 [68, 97]	83 [69, 95]	0.935	0.8
Creatinine (median [IQR])		81 [67, 97]	82 [66, 99]	80 [67, 95]	0.867	0.4
Glucose on admission (mmol/L) (median [IQR])		6.8 [6.1, 8.2]	6.8 [6.1, 8.1]	7 [6, 8.4]	0.636	1
Anticoagulants pre-stroke = Yes (%)		58 (12.1)	38 (14.4)	20 (9.3)	0.119	0.4
Antiplatelets pre-stroke = Yes (%)		106 (22.1)	64 (24.2)	42 (19.5)	0.261	0.4
NIHSS on admission (median [IQR])		11 [5, 18]	12 [6, 18]	10 [5, 18]	0.113	0.7
Time of symptom onset known (%)	No	63 (13.2)	38 (14.2)	35 (16.3)	0.173	0.4
	Wake up	69 (14.4)	33 (12.4)	37 (17.2)		
	Yes	347 (72.4)	195 (73.3)	143 (66.5)		
Onset-To-Door (min) (median [IQR])		166 [93, 356]	165 [91, 273]	169 [95, 518]	0.194	3.1
Etiology (%)	Cardiac embolism	170 (36.1)	103 (39.0)	64 (32.4)	0.008	2.1
	Cervical artery dissection	10 (2.1)	2 (0.8)	8 (3.9)		
	Large artery atherosclerosis	83 (17.6)	35 (13.3)	48 (23.2)		
	More than one possible etiology	19 (4.0)	11 (4.2)	8 (3.9)		
	Other determined etiology	25 (5.3)	19 (7.2)	6 (2.9)		
	Patent foramen oval	5 (1.1)	3 (1.1)	2 (1.0)		
	Unknown etiology	159 (33.8)	91 (34.5)	68 (32.9)		
Occlusion site (%)	ICA	89 (19.3)	46 (17.9)	43 (21.0)	0.312	4
	M1	168 (36.4)	105 (40.9)	63 (30.7)		
	M2	134 (29.0)	70 (27.2)	64 (31.2)		
	M3	17 (3.7)	7 (2.7)	10 (4.9)		
	A1-2	4 (0.9)	2 (0.8)	2 (1.0)		
	Posterior	50 (10.8)	27 (10.5)	23 (11.2)		
INTERVENTION						
Intravenous thrombolysis = Yes (%)		191 (39.9)	97 (36.5)	94 (44.1)	0.108	0.4
Maneuver count (median [IQR])		2 [1, 3]	2 [1, 3]	2 [1, 3]	0.107	5.8
eTICI (%)	0	11 (2.3)	6 (2.3)	5 (2.3)	0.042	0
	1	2 (0.4)	0 (0.0)	2 (0.9)		
	2a	21 (4.4)	10 (3.8)	11 (5.1)		

	2b50	54 (11.2)	24 (9.0)	30 (14.0)		
	2b67	95 (19.8)	49 (18.4)	46 (21.4)		
	2c	144 (29.9)	76 (28.6)	68 (31.6)		
	3	154 (32.0)	101 (38.0)	53 (24.7)		
eTICI dichotomized (%)	<eTICI3	327 (68.0)	165 (62.0)	162 (75.3)	0.003	0
	eTICI3	154 (32.0)	101 (38.0)	53 (24.7)		

EVT - endovascular therapy; FPDCT – flat-panel detector computed tomography; NIHSS - National Institutes of Health Stroke Scale; eTICI - extended Thrombolysis in Cerebral Infarction. Study group (EVT + FPDCT) encompasses all patients who have underwent FPDCT.

Table S3 Correlation Between eTICI (Core Lab) and the DOT Sign

	level	Overall	0	1	2a	2b50	2b67	2c	3	p
n		215	5	2	11	30	46	68	53	
DOT sign (%)	Negative	105 (48.8)	3 (60.0)	0 (0.0)	4 (36.4)	8 (26.7)	16 (34.8)	29 (42.6)	42 (84.9)	<0.001
	Positive	110 (51.2)	2 (40.0)	2 (100.0)	7 (63.6)	22 (73.3)	30 (65.2)	39 (57.4)	8 (15.1)	
Number of DOTs (median [IQR])		1 [0, 2]	0 [0, 1]	2 [1, 2]	1 [0, 3]	1 [1, 2]	1 [0, 2]	1 [0, 2]	0 [0, 0]	<0.001

Table S4 Correlation Between TICI (Operator) and the DOT Sign

	level	Overall	0	1	2a	2b	2c	3	p
n		215	7	3	9	54	41	101	
DOT sign (%)	Negative	105 (48.8)	4 (57.1)	0 (0.0)	3 (33.3)	16 (29.6)	16 (39.0)	66 (65.3)	<0.001
	Positive	110 (51.2)	3 (42.9)	3 (100.0)	6 (66.7)	38 (70.4)	25 (61.0)	35 (34.7)	
Number of DOTs (median [IQR])		1 [0, 2]	1 [0, 2]	2 [1, 2]	1 [0, 3]	1 [0, 2]	1 [0, 2]	0 [0, 1]	<0.001

Table S5 Sensitivity and Specificity of the DOT sign

	Core lab graded eTICI	
DOT sign	eTICI3	eTICI<3
Negative	45	60
Positive	8	102

DOT sign (positive/negative) was compared to the core lab eTICI score as the current reference standard in evaluation of residual vessel occlusion (eTICI3/eTICI<3). Sensitivity identifies actual positive cases which were correctly predicted as positive, while specificity identifies actual negative cases which were predicted correctly as negative. Sensitivity: 0.63 (95%CI 0.55 – 0.70); Specificity: 0.85 (95%CI 0.72 – 0.93); Positive predictive value: 0.93 (95%CI 0.86 – 0.97); Negative predictive value: 0.43 (95%CI 0.33 – 0.53); Accuracy: 0.68 (95%CI 0.62 – 0.75).

Table S6 Per-vessel Analysis of the DOT Sign

	Number of vessel occlusions on DSA	
Number of DOT signs	One	**More than one**
One	39	17
More than one	68	91

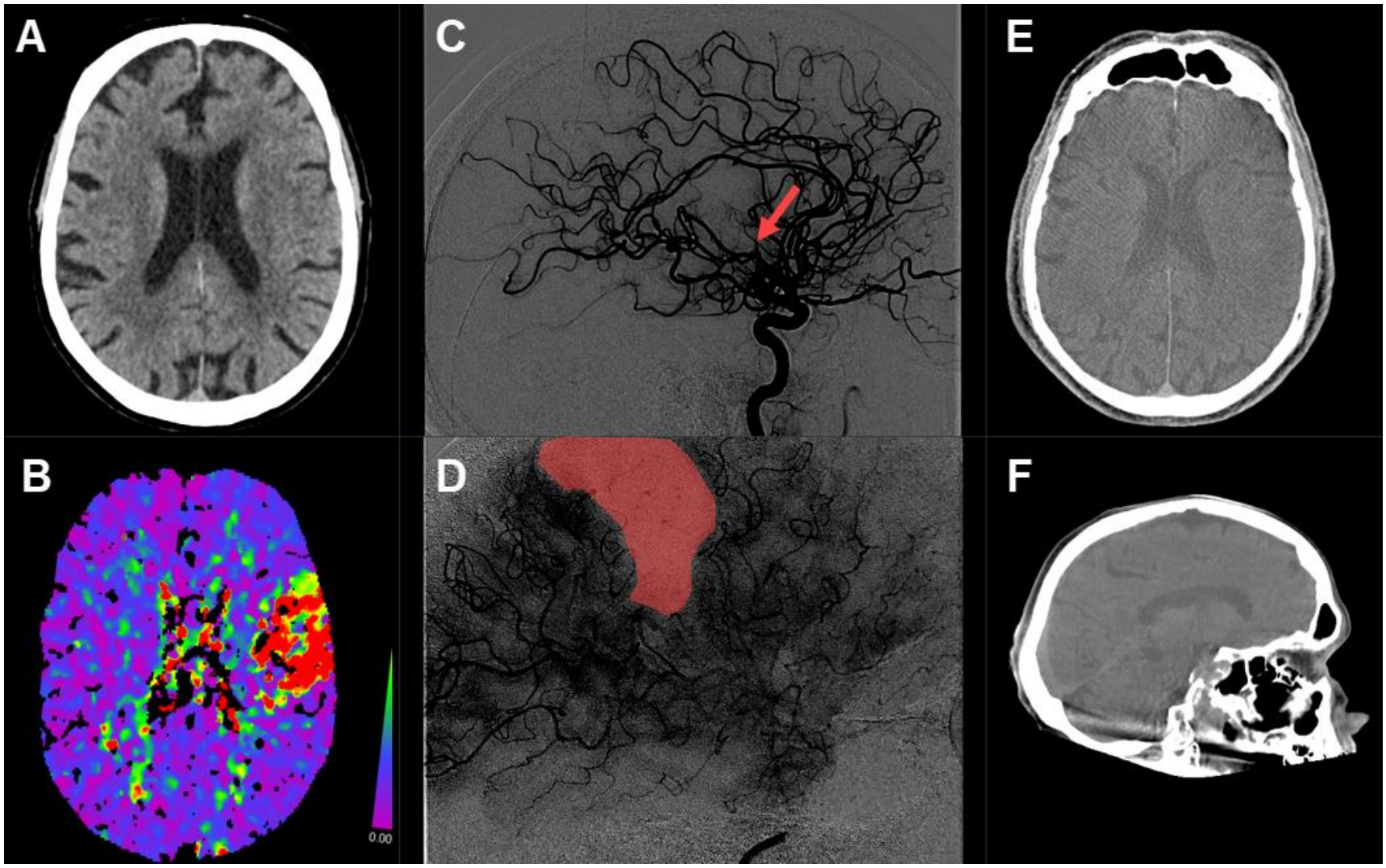
DSA: digital subtraction angiography; FPDCT: flat-panel detector computed tomography. For the per-vessel analysis, DOT sign from FPDCT imaging was spatially correlated to the corresponding location on the final DSA runs. Only cases where all the DOT signs could be directly superposed on the final DSA run were evaluated as concordant. Re-reviewing images from the FPDCT enabled detection of additional occlusions in 68/107 (64%) of total cases when compared to DSA alone.

Table S7 Multivariate regression analysis for mRS 0-2

	mRS 0 -2			mRS 0 -2*		
Factors	Adjusted Odds Ratios	95% CI	P-Value	Adjusted Odds Ratios	95% CI	P-Value
Age	0.97	0.94 – 1.00	**0.043**	0.96	0.93 – 1.00	**0.027**
Sex	1.81	0.88 – 3.74	0.106	1.83	0.87 – 3.84	0.108
Intravenous Thrombolysis	1.25	0.61 – 2.61	0.544	1.20	0.57 – 2.55	0.632
Onset-to-Admission (h)	0.99	0.94 – 1.04	0.535	0.99	0.95 – 1.05	0.742
NIHSS On Admission	0.92	0.87 – 0.97	**0.001**	0.92	0.87 – 0.96	**0.001**
Vessel occlusion site (reference category: ICA)	-	-	-	-	-	-
M1	2.12	0.84 – 5.52	0.116	2.19	0.85 – 5.80	0.108
M2	0.95	0.35 – 2.53	0.923	1.15	0.41 – 3.18	0.787
M3	0.78	0.11 – 5.04	0.798	1.09	0.16 – 6.70	0.929
A1-2	0.24	0.01 – 7.40	0.361	0.27	0.01 – 11.42	0.470
Posterior vessel occlusion	2.25	0.54 – 11.86	0.290	1.87	0.44 – 9.91	0.417
DOT sign (positive)	0.43	0.21 – 0.87	**0.021**	0.59	0.27 – 1.26	0.173
eTICI				1.58	1.17 – 2.16	**0.003**

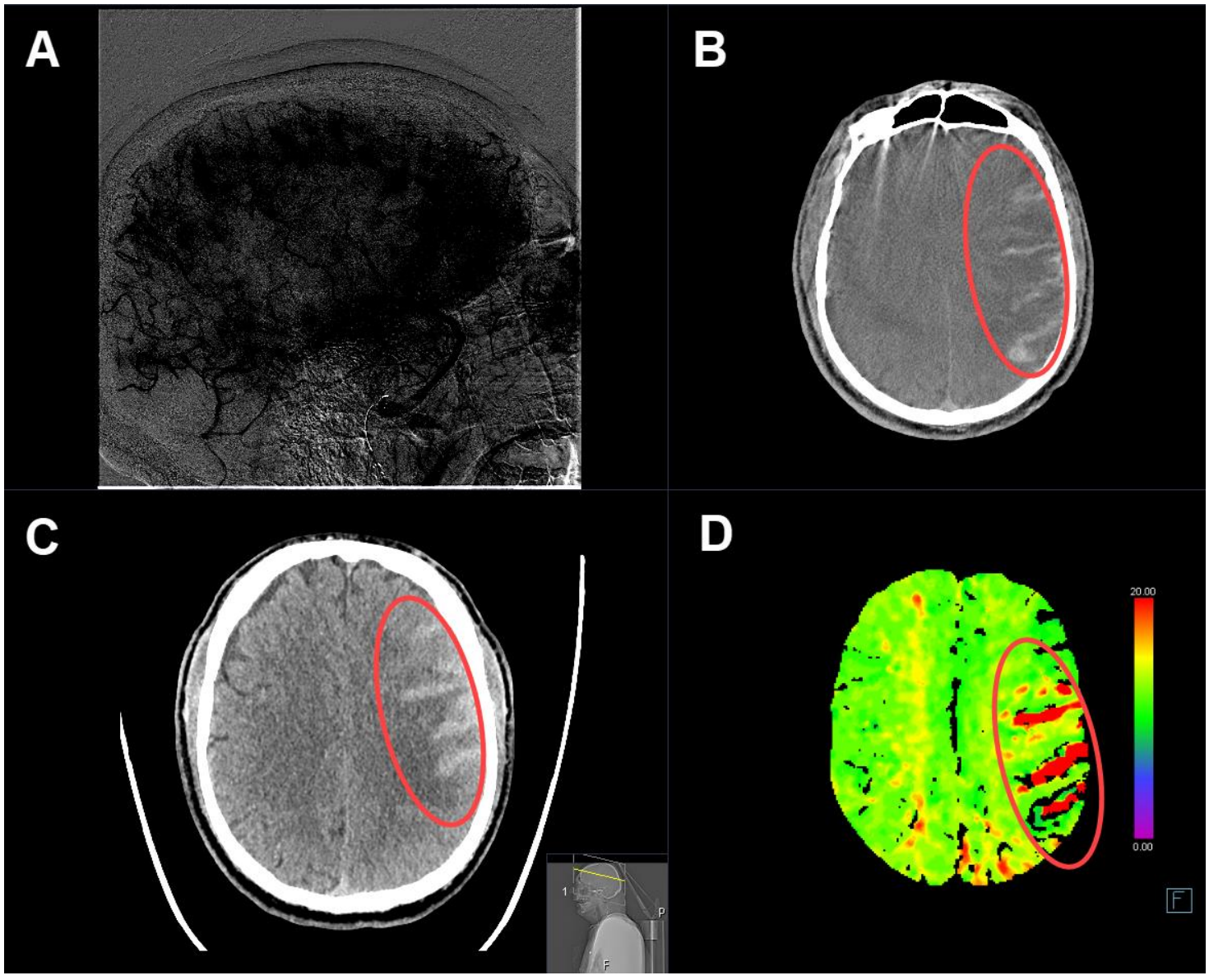
mRS: modified Rankin scale; NIHSS: National Institutes of Health Stroke Scale; ICA: internal carotid artery; eTICI: expanded Thrombolysis in Cerebral Infarction.*Sensitivity analysis adjusted for the eTICI score. In the multivariate adjusted regressions analysis positive DOT sign was associated with lower odds of achieving mRS 0-2 (aOR 0.4, 95%CI 0.2 – 0.8). In the *sensitivity analysis which was adjusted for the eTICI score, point estimates for the DOT sign showed same direction for the mRS 0-2 but without statistical significance (aOR 0.6, 95%CI 0.3 – 1.3).

Figure S1 Negative DOT sign



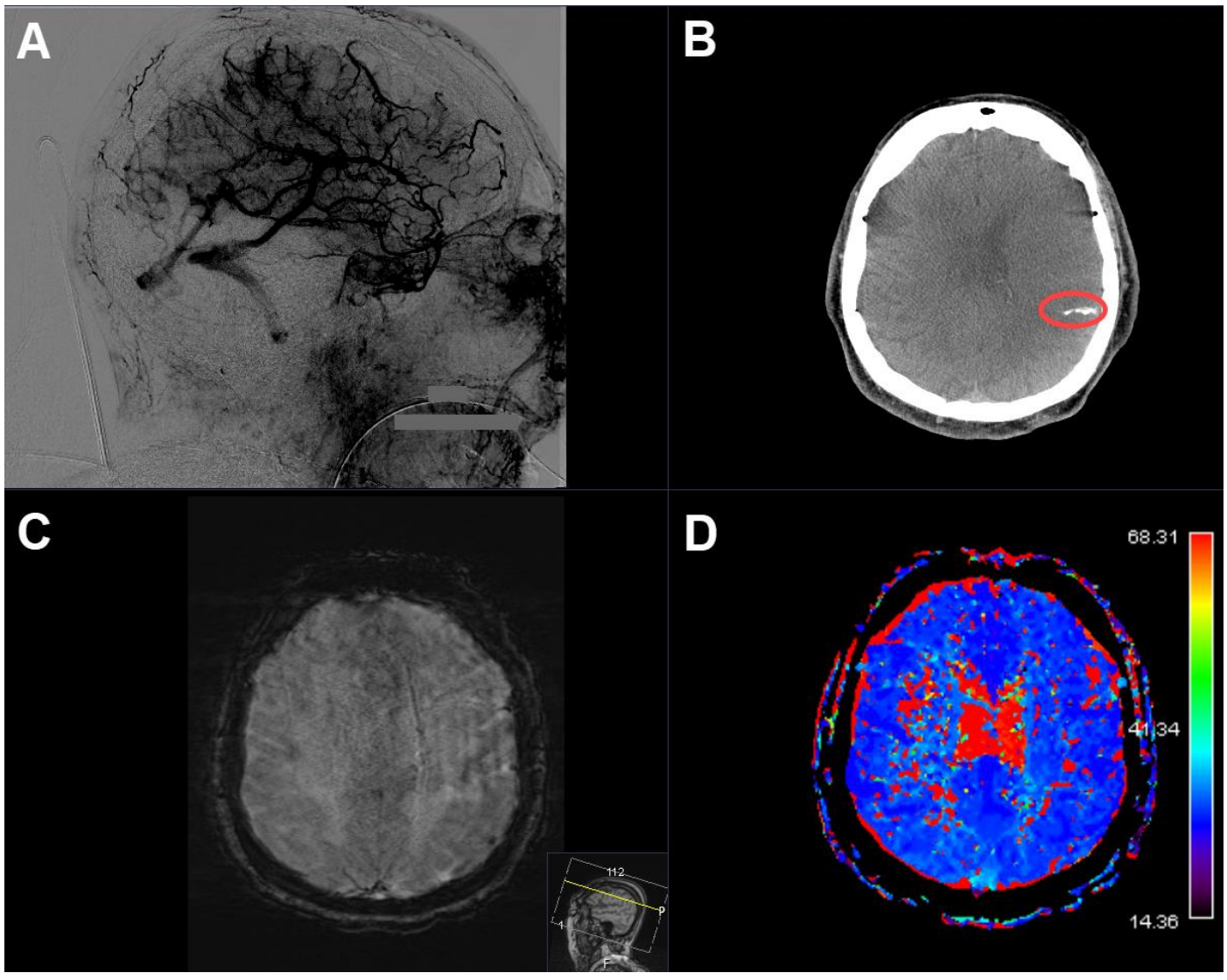
CT: computed tomography; TTP: time to peak; MCA: middle cerebral artery; FPDCT: flat-panel detector CT. (A-B) Admission imaging shows already demarked infarct area on CT and TTP corresponding to a left-side M2 MCA. (C) First angiography run confirms occlusion location in the M2 branch of the MCA (red arrow). (D) Final angiography imaging shows partial reperfusion (eTICI2b50, non-perfused area colored in red) with a residual MCA occlusion. (E) Immediate post-interventional FPDCT shows negative DOT sign in the area which directly corresponds to the position of the residual vessel occlusion. (F) Sagittal projection of the FPDCT imaging revels the same finding with a negative DOT sign.

Figure S2 Contrast Extravasation on FPDCT



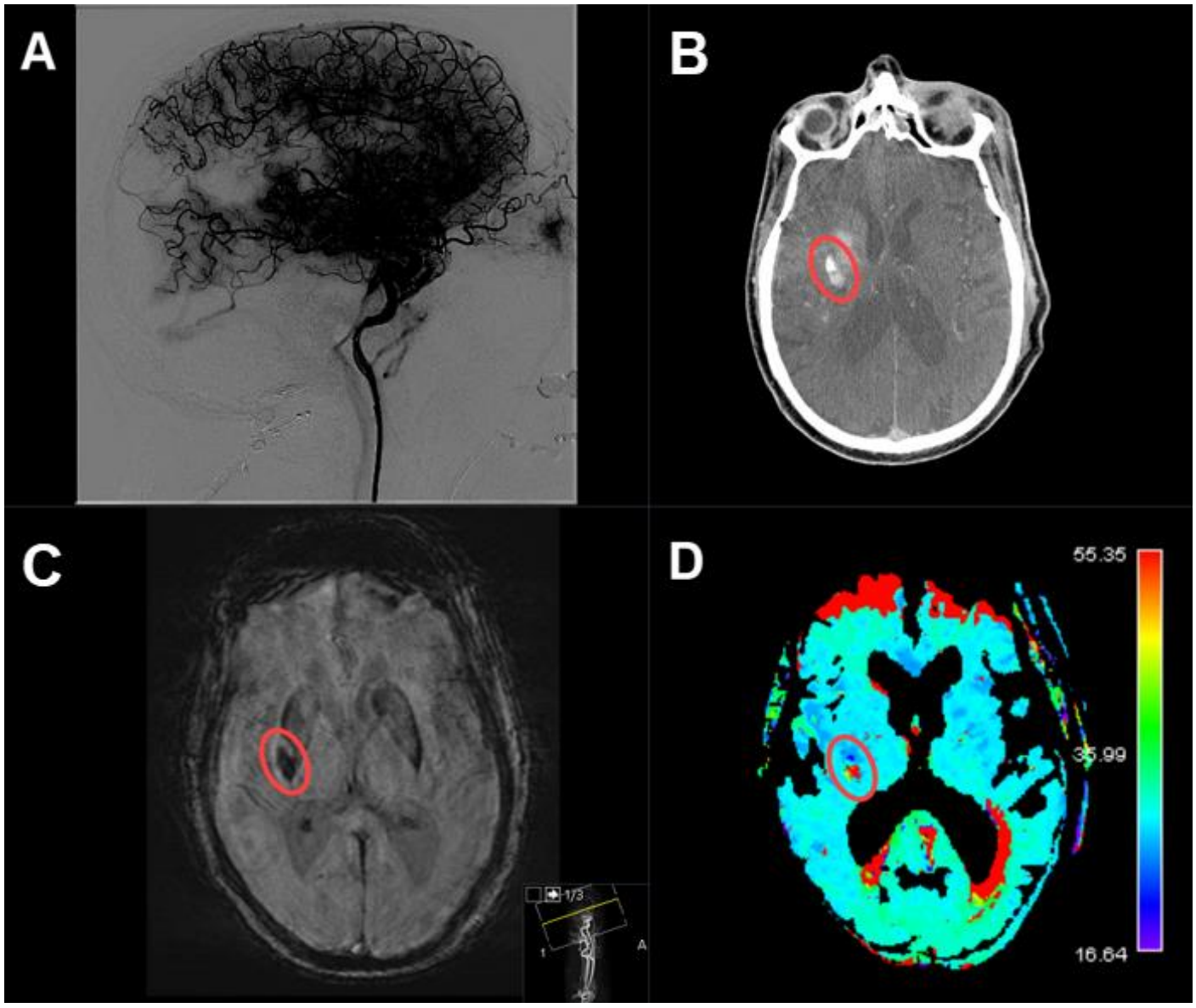
MCA: middle cerebral artery; eTICI: expanded Thrombolysis in Cerebral Infarction; FPDCT: flat-panel detector CT; TTP: time to peak. (A) Final angiography imaging of the initial left-side M1 MCA occlusion showing complete reperfusion (eTICI3) of the initial target territory. (B) Immediate post-interventional FPDCT shows a hyperdense signal which directly corresponds the initial target territory (red circle). (C) On the 24 hour follow-up FPDCT we observe demarcated territorial infarct area in the left mediastromal region with postinterventional contrast extravasation (red circle). (D) Contrast extravasation is also seen as signal decrease on the TTP perfusion imaging without a gradual delay cascade. This patient would not be classified as having a positive DOT sign as these findings are due to postinterventional contrast extravasation.

Figure S3 Subarachnoid Hyperdensities on FPDCT



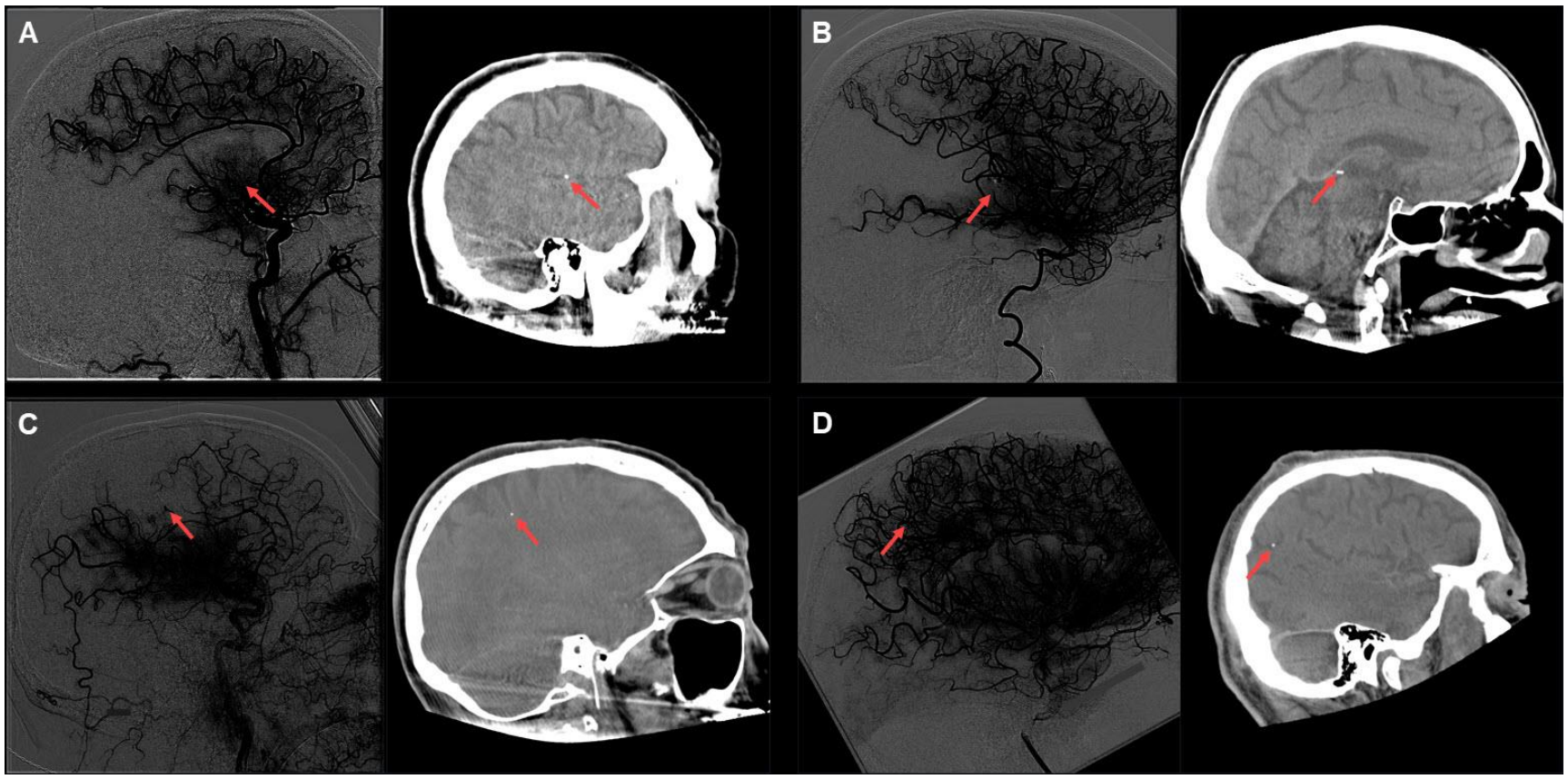
MCA: middle cerebral artery; eTICI: expanded Thrombolysis in Cerebral Infarction; FPDCT: flat-panel detector CT; SWI: susceptibility weighted imaging; Tmax: time to maximum. (A) Final angiography imaging of the initial left-side M1 MCA occlusion showing complete reperfusion (eTICI3) of the initial target territory. (B) Immediate post-interventional FPDCT shows a hyperdense signal in the initial target territory, confined to and filing the subarachnoid space (red circle). (C) On the 24 hour follow-up SWI we do not observe a loss of signal in the area of interest, suggesting an absence of hemorrhage, (D) nor do we see any perfusion deficit on follow-up Tmax which suggests an absence of a residual distal occlusion or new infarct. This patient would not be classified as having a positive DOT sign as these findings are due to postinterventional subarachnoid hyperdensities.

Figure S4 Hemorrhage on FPDCT



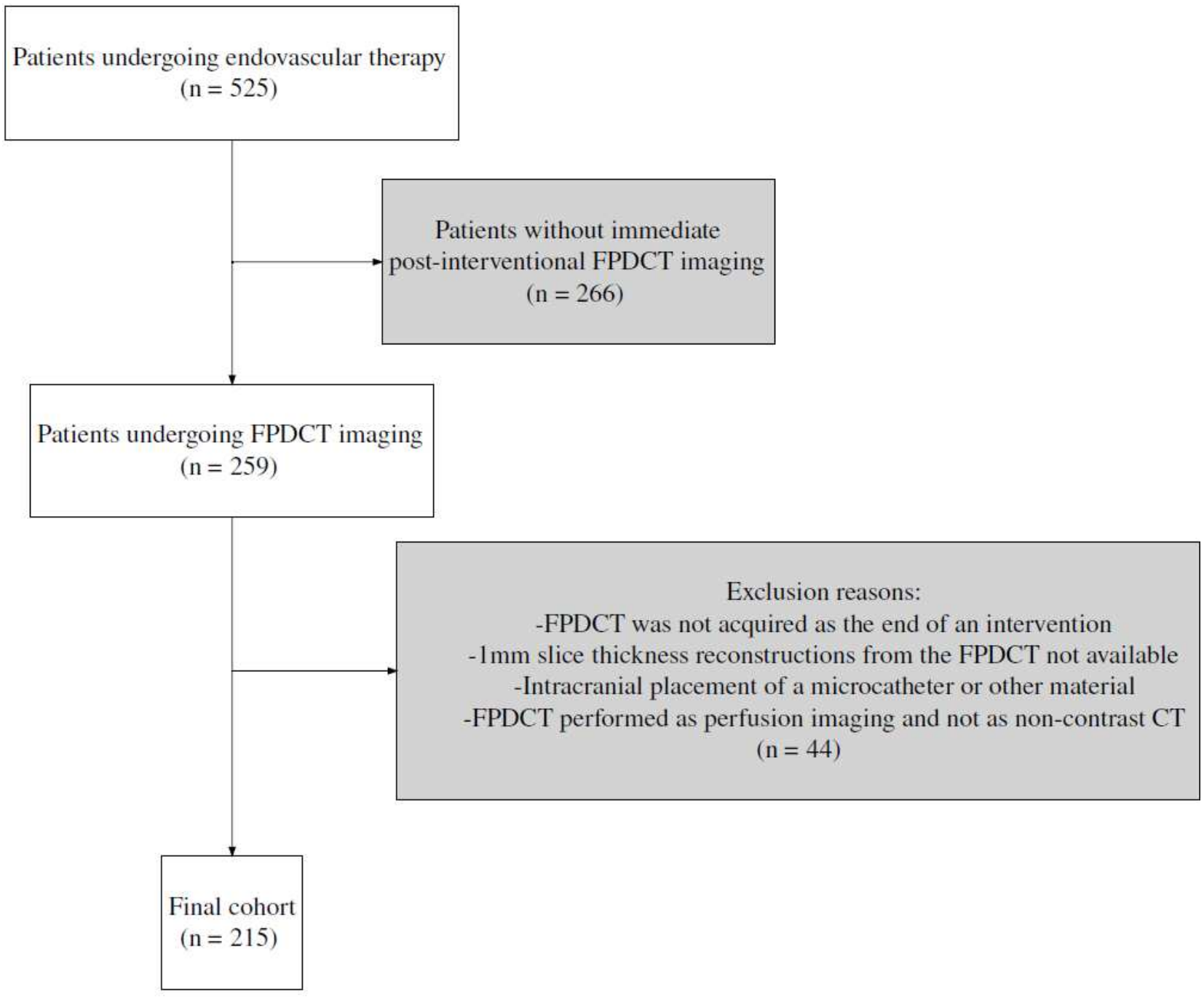
MCA: middle cerebral artery; eTICI: expanded Thrombolysis in Cerebral Infarction; FPDCT: flat-panel detector CT; SWI: susceptibility weighted imaging; TTP: time to peak. (A) Final angiography imaging of the initial right-side M1 MCA occlusion showing incomplete reperfusion (eTICI2b50) of the initial target territory. (B) Immediate post-interventional FPDCT shows a hyperdense signal directly corresponding to the initial target territory (red circle). (C) On the 24 hour follow-up SWI we observe a loss of signal in the area of interest (red circle). (D) TTP map also shows severe perfusion delay, without a gradual delay cascade. This patient would not be classified as having a positive DOT sign, because these findings are due to blood product accumulation and hemorrhagic tissue transformation.

Figure S5 Concordance Between the Vessel Occlusion and the DOT Sign



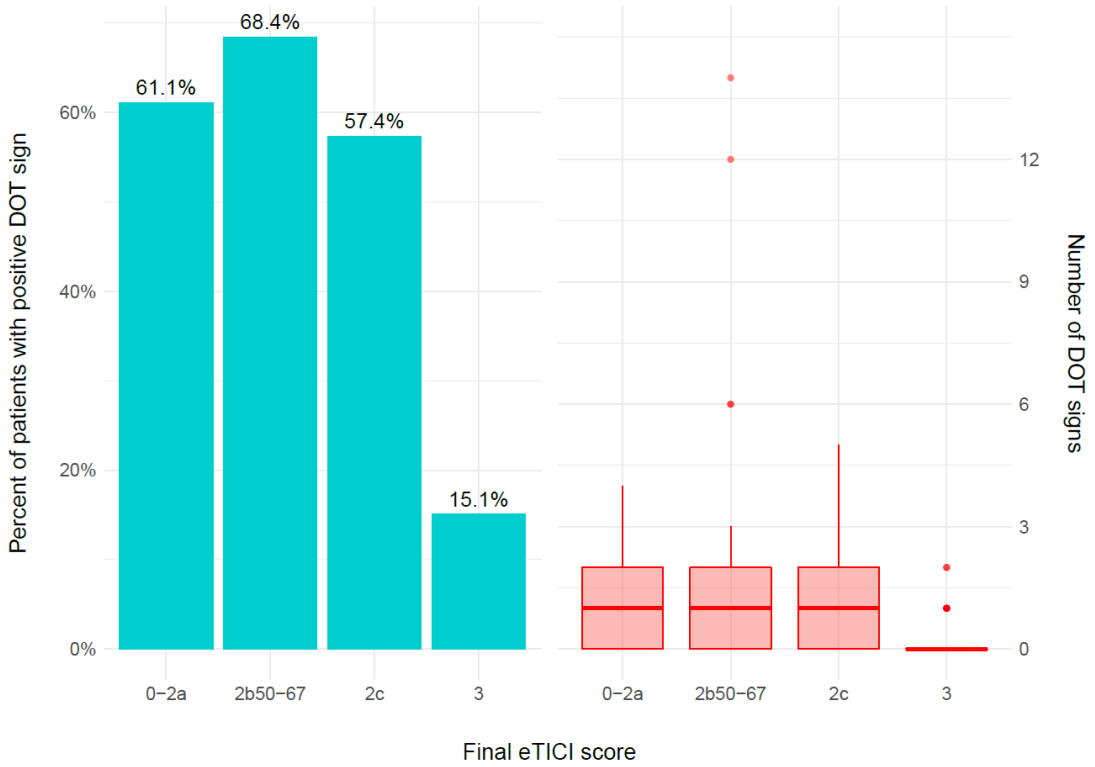
FPDCT: flat-panel detector CT; DSA: digital subtraction angiography. For the per-vessel analysis, DOT sign from FPDCT imaging was spatially correlated to the corresponding location on the final DSA runs. Only cases where all the DOT signs could be directly superposed on the final DSA run were evaluated as concordant. (A) Patient with initial ICA occlusion and residual occlusion in one of the MCA-M3 branches (eTICI 2b67). (B) Patient with an initial MCA-M1 occlusion and residual occlusion in the MCA-M3 branch (eTICI 2b50). (C) Patient with an initial MCA-M1 occlusion and residual occlusion in the distal branch (eTICI 2b67). (D) Patient with an initial MCA-M1 occlusion and small residual occlusion in the occipital region (eTICI 2c).

Figure S6 Flow Chart



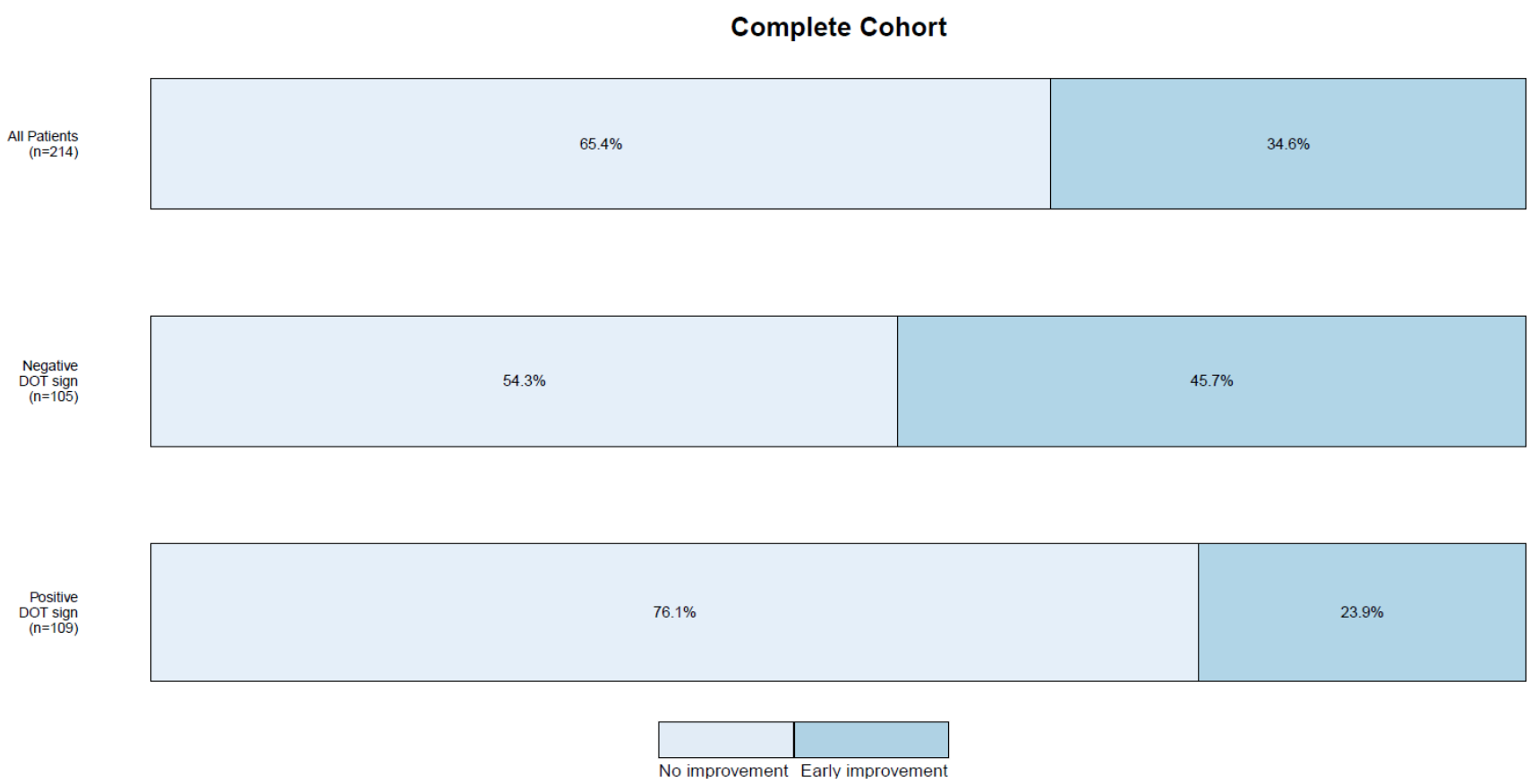
FPDCT: flat-panel detector computed tomography

Figure S7 Positive DOT sign across eTICI scores



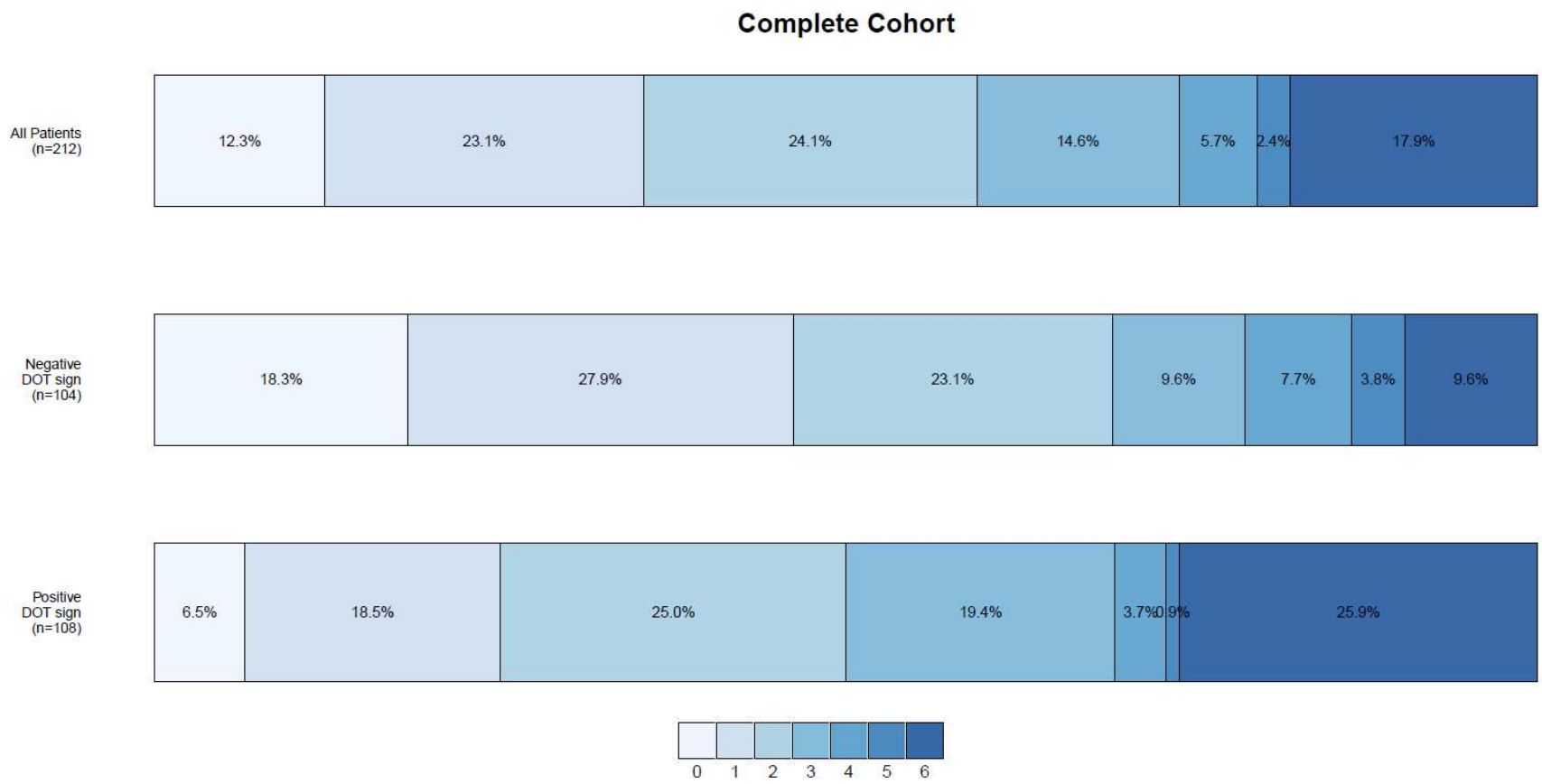
Patients with unsuccessful (eTICI 0-2a), partial (eTICI 2b50-67) or near complete (eTICI 2c) reperfusion were more likely to have a positive DOT sign on follow-up flat-panel detector computed tomography (FPDCT) when compared to patients with complete reperfusion (eTICI 3).

Figure S8 Rates of Strong Neurological Improvement in the Entire Cohort



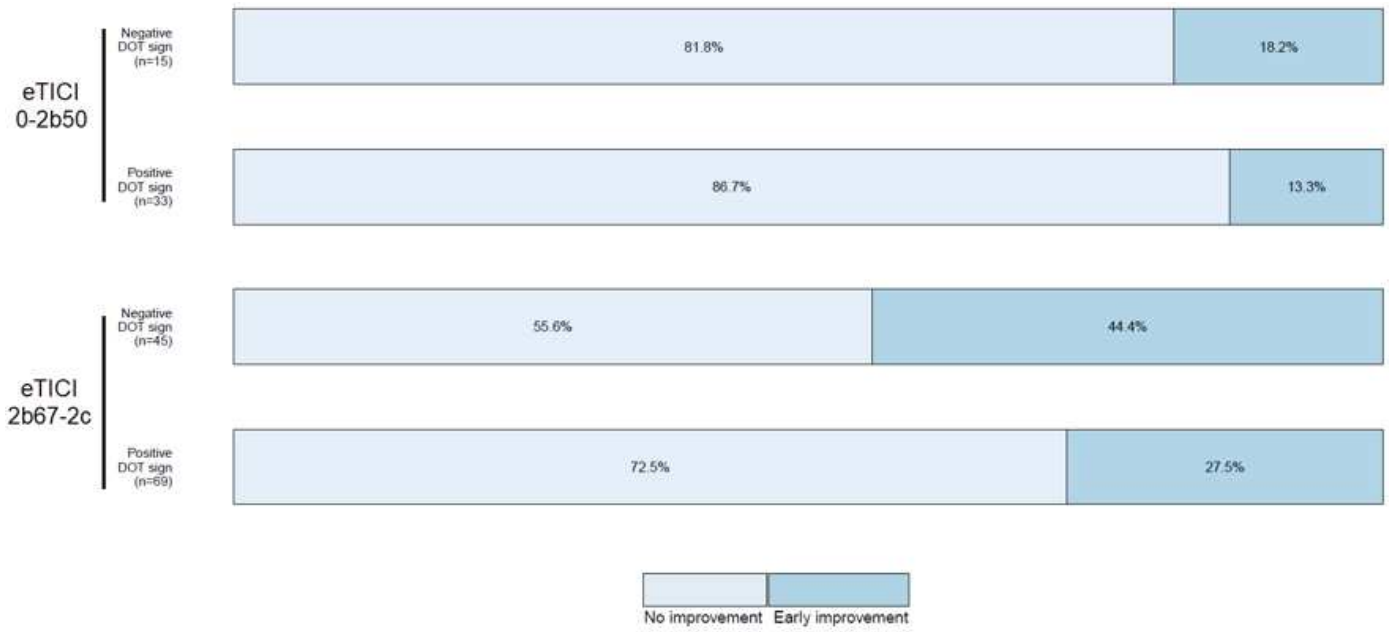
NIHSS: National Institutes of Health Stroke Scale. Early improvement or strong neurological improvement (c-NIHSS) was defined as either difference between NIHSS at discharge and admission ≥8 points or NIHSS at discharge≤1. Patients with the negative DOT sign had higher likelihood of achieving strong neurological improvement when compared to patients with a positive DOT sign (45.7% vs 23.9%; p=0.001).

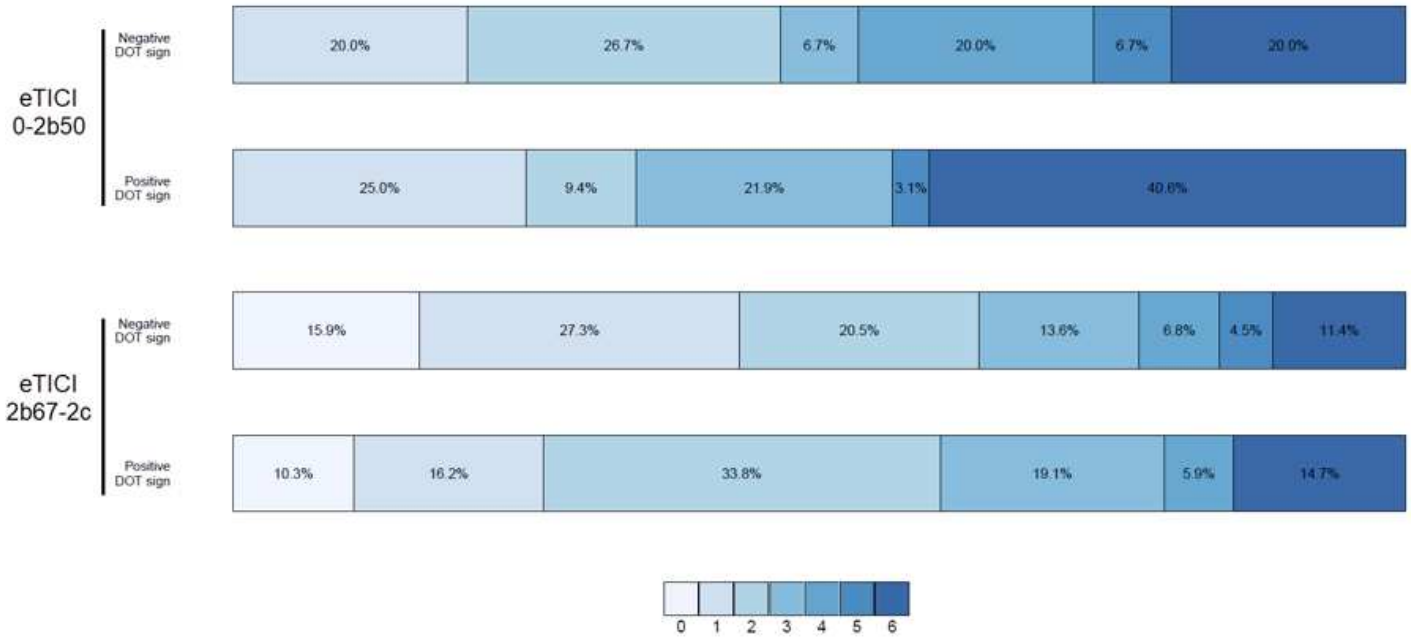
Figure S9 Rates of Functional Independence in the Entire Cohort



Functional independence was defined as the modified Rankin scale (mRS) score 0-2 at 3 months after the index event. Patients with the negative DOT sign had higher likelihood of achieving functional independence when compared to patients with a positive DOT sign (45.7% vs 23.9%; p=0.001).

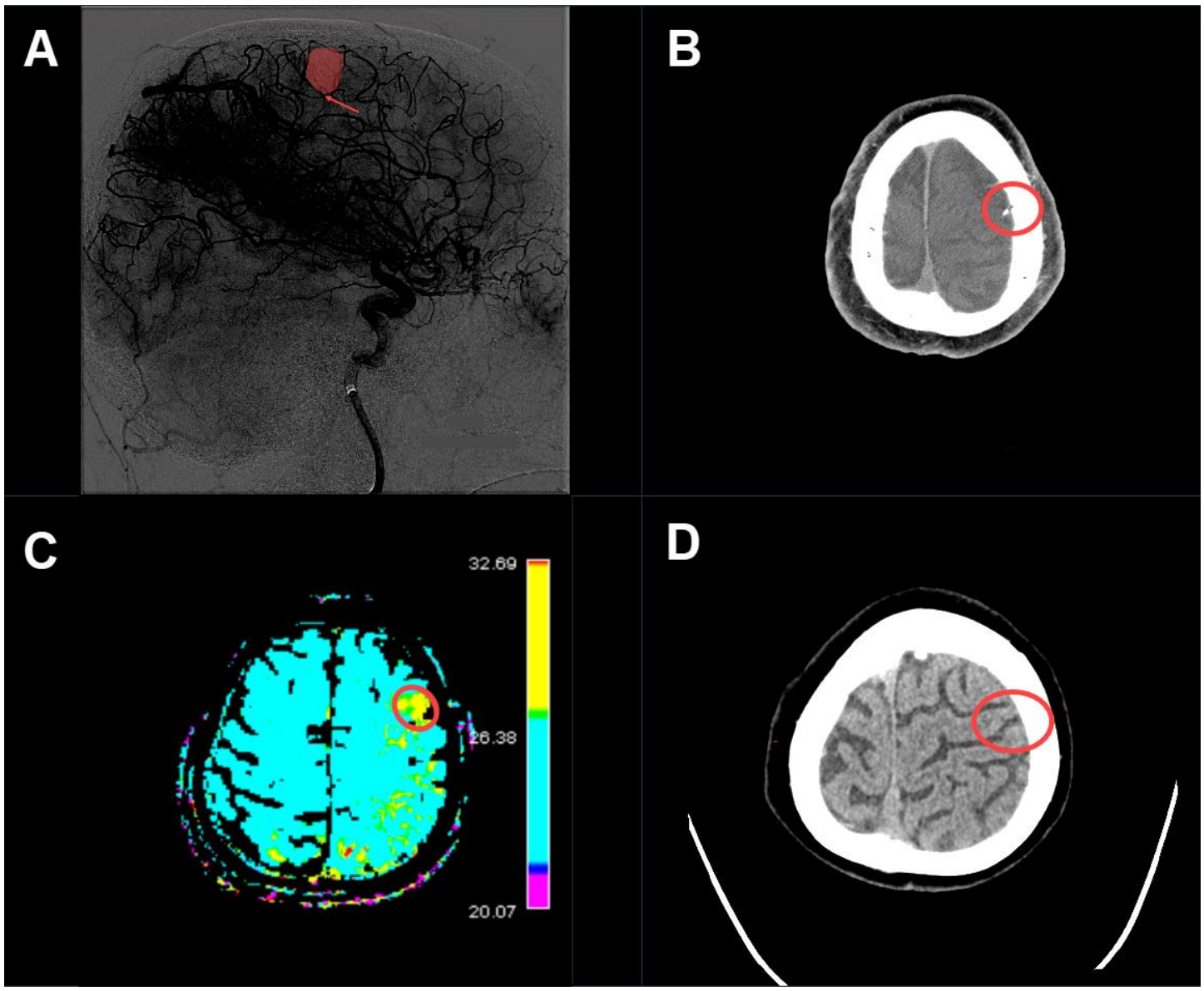
Figure S10 Outcome Stratified by eTICI





Rates of early improvement or strong neurological improvement (c-NIHSS) and functional independence (mRS 0-2) stratified across the eTICI score dichotomized at eTICI2b50. Across the eTICI strata, patients with the negative DOT sign had higher likelihood of better outcome.

Figure S11 Positive DOT sign Closely Located to the Skull



MCA: middle cerebral artery; eTICI: expanded Thrombolysis in Cerebral Infarction; FPDCT: flat-panel detector CT; TTP: time to peak. (A) Final angiography imaging of the initial left-side M2 MCA occlusion showing incomplete reperfusion (eTICI2c) of the initial target territory (red arrow). (B) Immediate post-interventional FPDCT shows a hyperdense signal, which directly corresponds to the initial target territory. However, due to the proximity of the skull, the hypdense signal could be overlooked and considered part of the skull area (red circle). (C) On the 24 hour follow-up TTP map we see perfusion delay with gradual delay cascade suggestive of persisting vessel occlusion (red circle). (D) Taking a look at the admission non-contrast CT, it can be confirmed that observed hyperdensity from FPDCT is not part of the skull but in fact a positive DOT sign.