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Abstract:

Aim:

To assess the clinical performance of a commercially available machine learning (ML) algorithm in acute stroke.

Materials and Methods:

CT and CT angiography (CTA) studies of 104 consecutive patients (43 females, age range 19-93, median age 62) performed for suspected acute stroke at a single tertiary institution with real-time ML software analysis (RAPID™ ASPECTS and CTA) were included. Studies were retrospectively reviewed independently by two neuroradiologists in a blinded manner.

Results:

The cohort included 24 acute infarcts and 16 large vessel occlusions (LVO). RAPID™ ASPECTS interpretation demonstrated high sensitivity (87.5%) and NPV (87.5%) but very poor specificity (30.9%) and PPV (30.9%) for detection of acute ischaemic parenchymal changes. There was a high percentage of false positives (51.1%). In cases of proven LVO, RAPID™ ASPECTS showed good correlation with neuroradiologists' blinded independent interpretation, Pearson correlation coefficient = 0.96 (both readers), 0.63 (RAPID™ vs reader 1), 0.69 (RAPID™ vs reader 2).

RAPID™ CTA interpretation demonstrated high sensitivity (92.3%), specificity (85.3%), and negative predictive (NPV) (98.5%) with moderate positive predictive value (PPV) (52.2%) for detection of LVO (N=13). False positives accounted for 12.5% of cases, of which 27.3% were attributed to arterial stenosis.

Conclusion:

RAPID™ CTA was robust and reliable in detection of LVO. Although demonstrating high sensitivity and NPV, RAPID™ ASPECTS interpretation was associated with a high number of false positives, which decreased clinicians' confidence in the algorithm. However, in cases of proven LVO, RAPID™ ASPECTS performed well and had good correlation with neuroradiologists' blinded interpretation.

Machine-learning algorithm in acute stroke: real-world experience

N. Chan[a,b], N. Sibtain[a], T. Booth[a,c], P. de Souza[d], S. Bibby[a], Y.-H. Mah[e], J. Teo[e], J. M. U-King-Im[a]

[a]Department of Neuroradiology, King's College Hospital, London, UK

[b]Department of Interventional Neuroradiology, The Royal London Hospital, London, UK

[c]School of Biomedical Engineering and Imaging Sciences, King's College London, London, UK

[d]Department of Neuroradiology, The Royal London Hospital, London, UK

[e]Department of Neurology, King's College Hospital, London, UK

*Guarantor and correspondent: N. Chan, Department of Interventional Neuroradiology, The Royal London Hospital, Whitechapel Road, London E1 1BB, UK. Tel.: ?????

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E-mail address: Nathan.chan3@nhs.net

ABSTRACT

AIM: To assess the clinical performance of a commercially available machine-learning (ML) algorithm in acute stroke.

MATERIALS AND METHODS: Computed tomography (CT) and CT angiography (CTA) studies of 104 consecutive patients (43 women, age range 19–93 years, median age 62 years) performed for suspected acute stroke at a single tertiary institution with real-time ML software analysis (RAPID ASPECTS and CTA) were included. Studies were reviewed retrospectively and independently by two neuroradiologists in a blinded manner.

RESULTS: The cohort included 24 acute infarcts and 16 large-vessel occlusions (LVO). RAPID ASPECTS interpretation demonstrated high sensitivity (87.5%) and negative predictive value (NPV; 87.5%) but very poor specificity (30.9%) and positive predictive value (PPV; 30.9%) for detection of acute ischaemic parenchymal changes. There was a high percentage of false positives (51.1%). In cases of proven LVO, RAPID ASPECTS showed good correlation with neuroradiologists' blinded independent interpretation (Pearson correlation coefficient=0.96 [both readers], 0.63 [RAPID versus reader 1], 0.69 [RAPID versus reader 2]). RAPID CTA interpretation demonstrated high sensitivity (92.3%), specificity (85.3%), and NPV (98.5%) with low PPV (52.2%) for the detection of LVO (*n*=13). False positives accounted for 12.5% of cases, of which 27.3% were attributed to arterial stenosis.

CONCLUSION: RAPID CTA was robust and reliable in detection of LVO. Although demonstrating high sensitivity and NPV, RAPID ASPECTS interpretation was associated with a high number of false positives, which decreased clinicians' confidence in the algorithm; however, in cases of proven LVO, RAPID ASPECTS performed well and had good correlation with neuroradiologists' blinded interpretation.

INTRODUCTION

Mechanical thrombectomy (MT) is the standard of care for patients with proximal anterior circulation occlusions. This has become accepted after the publication of several clinical trials in 2015[1]. Reducing the time to diagnosis and treatment of stroke patients is an important part of any stroke MT service. Delays in treatment lead to worse clinical outcomes. In a meta-analysis of five randomised trials, rates of functional independence after thrombectomy were 64% with reperfusion at 3 h versus 46% with reperfusion at 8 h[2]. Decision-support tools in the form of artificial intelligence (AI) algorithms can help reduce times to treatment, potentially improving outcomes[3].

AI and machine-learning (ML) algorithms are a rapidly expanding field in acute stroke imaging and commercial software packages have been developed for automated assessment of Alberta Stroke Program Early CT Score (ASPECTS), identification of large-vessel occlusions (LVO) on computed tomography (CT) angiography (CTA) and interpretation of CT perfusion (CTP)[3]. These are often used as decision-support tools by radiologists; however, the real-world performance of many AI/ML packages remains to be determined, especially due to known generalisability issues of AI/ML models or when encountering out-of-dataset scenarios[3].

Several types of ML algorithms are available, which provide different methods for adjusting feature weights and assumptions about data to enable optimisation of outputs. The more common algorithm types include neural networks, k-nearest neighbours, support vector machines, decision trees, and naive Bayes algorithm[4]. The more widely used commercial algorithms include RAPID ASPECTS and LVO software, which utilises a random forest learning algorithm (a form of decision tree algorithm)[3], Brainomix and Viz.ai, which also provide ASPECTS and LVO assessment using convoluted neural network (CNN) algorithms[3].

iSchemaView RAPID initially developed software that was validated for perfusion imaging in stroke. The RAPID CTP software received US Food and Drug

Administration (FDA) approval in 2013 and was used in large LVO trials such as DEFUSE 3 and DAWN[3,5,6]. Automated LVO detection on CTA and ASPECTS scoring components were subsequently incorporated into the software package. At the authors' institution, the RAPID CTP, CTA, ASPECTS software package is used in clinical practice as part of the MT pathway.

The main aims of the present study were to assess the diagnostic performance of the ASPECTS and CTA components of the RAPID software package in a real-world setting. The diagnostic performance of the AI algorithm was compared with consensus expert neuroradiologists' interpretation in a series of consecutive patients being assessed for possible acute stroke and MT at a busy hyper-acute stroke unit.

MATERIALS AND METHODS

The study was assessed using the health research authority decision tool and due to the retrospective design, deemed not to require ethical approval. Local registration as a service evaluation project was approved.

Patient selection and AI/ML interpretation

The CT and CTA images performed to exclude stroke for 104 consecutive adult patients presenting from January to March 2021 at a single tertiary neuroscience institution were analysed. Only patients considered for thrombolysis or MT were included. In order to be considered for thrombolysis or MT, patients were required to be previously independent with modified Rankin Scale 0–2, with a presentation National Institutes of Health Stroke Scale (NIHSS) of ≥5, and a time of onset between 4.5 and 23 h. Patients with posterior circulation infarct, acute intracranial haemorrhage, or imaging performed for anterior or posterior circulation dissection were excluded. The images were analysed by RAPID software (iSchemaView, Menlo Park, CA, USA) at the time of scanning. The RAPID AI ASPECTS and CTA output was available on the picture archiving and communication system (PACS) and visible to clinicians during the acute presentation.

CT and CTA

CT and CTA was performed on a LightSpeed VCT 64-section CT system (GE Healthcare). CT head images were obtained from the skull base to the vertex at a thickness of 0.625 mm (120 kVp, automatic tube current). CTA images were obtained from the aortic arch through the vertex with the same parameters. Intravenous access was through an antecubital vein by using an 18- or 20-G angiocatheter. A total of 100 to 120 ml iohexol (Omnipaque 300; GE Healthcare) or iodixanol (Visipaque 320; GE Healthcare) was injected at a rate of 4–5 ml/s with a 17-second delay or the use of SmartPrep software (GE Healthcare) at the pulmonary artery.

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Image analysis

The CT and CTA images were reviewed retrospectively and independently by two experienced neuroradiologists. Reader 1 was a neuroradiology fellow and a fellow of the Royal College of Radiologists. Reader 2 was a neuroradiologist with >10 years of experience as a consultant. Both readers were blinded to the report and the RAPID software interpretation. Any differences in opinion were resolved in consensus. LVO was defined as terminal internal carotid artery (ICA) or middle cerebral artery (MCA) segment M1 occlusion.

Statistical analysis

Statistical analysis was performed using commercially available software (IBM SPSS for Windows, version 23.0.0; SPSS, Chicago, IL, USA). Correlation between RAPID ASPECTS, reader 1 and reader 2 was performed using the Pearson correlation coefficient.

RESULTS

The cohort of 104 patients included 43 women, with an age range of 19–93 years and a median age of 62 years. The first patient presented on 3 January 2021 and the patient was scanned on 19 March 2021. There were 24 acute infarcts identified on the presentation imaging, with 16 LVOs. The 24 acute infarcts included 21 MCA territory, two ICA territory, one MCA perforator, and one corona radiata infarcts. Fig. 1 is a consort diagram illustrating the patients included in the study. Five patients were excluded: one patient that had a cervical ICA dissection, another patient was suffering from basilar artery occlusion; three patients with lobar haemorrhage were excluded from the ASPECTS analysis. Of note, however, all three of these were mis-identified as infarcts by RAPID ASPECTS (ASPECTS scores 6, 7, and 8).

CT

RAPID ASPECTS interpretation was available for 92 of the 99 patients. RAPID ASPECTS demonstrated high sensitivity (87.5%) and negative predictive value (NPV), but very poor specificity (30.9%) and positive predictive value (PPV) for detection of acute ischaemic parenchymal changes. There was a high percentage of false positives (51.1%, 47 of 92). Table 1 demonstrates the sensitivity, specificity, PPVs and NPVs based on the data provided.

In 25.5% (12 of 47) of the false-positive cases RAPID ASPECTS reported infarcts on the wrong hemisphere, when taking into account patients' clinical presentation and follow-up imaging. In the majority of false-positive cases (82.9%, 39 of 47), the ASPECTS score provided by RAPID was ≥7. In 61.7% (29 of 47) of cases, the ASPECTS score was ≥8. In only 6.4% (3 of 47) cases had an ASPECTS score ≤3. This would suggest that RAPID ASPECTS often erroneously over-called (generally 1–2) isolated territories of ischaemia in otherwise normal CT head examinations.

In cases of proven LVO, RAPID ASPECTS identified the correct hemisphere in all cases (13/13) and had moderate to strong correlation with neuroradiologists' interpretation, e.g., Fig. 2[7]. The Pearson correlation coefficient was 0.63 (RAPID versus reader 1), 0.69 (RAPID versus reader 2) and 0.96 (reader 1 versus reader 2). Fig. 3 demonstrates the correlation between RAPID and the mean ASPECTS score of both readers with a 95% confidence interval marked. Vascular hyperdensity affecting MCA M1–M3 branches was seen in 11 cases and of these RAPID ASPECTS identified the correct side in 10. The mean ASPECTS score in cases of proven LVO was 5 (range 0–9). ASPECTS scores determined by both readers were very similar, with only minor differences of 1 or 2 points, which was more common in LVO-positive cases (10 of 16).

Follow-up CT or magnetic resonance imaging (MRI) was available for 70 of 99 patients. Recent infarcts were demonstrated in 34 of 70 patients on follow-up imaging, including 10 cases missed on the presentation imaging by the reporting radiologist, reader 1 and reader 2, but present on follow-up imaging. In 16 cases, these were missed by both readers. In 11 of 16 cases, these affected the supratentorial white matter, thalamus, brainstem, or cerebellum. RAPID ASPECTS identified one cortical infarct missed by both that was identified on follow-up MRI.

Follow-up imaging was available for eight patients with proven LVO. ASPECTS score at follow-up correlated better with reader interpretation than RAPID ASPECTS, Pearson *R*=0.71 (reader 1 versus follow-up), 0.70 (reader 2 versus follow-up) and 0.24 (RAPID ASPECTS versus follow-up).

CTA

RAPID CTA interpretation was available for 88 of 102 cases, which included 13 of 16 LVOs. The RAPID CTA software demonstrated high sensitivity (92.3%), specificity (85.3%), and NPV (98.5%) for detection of LVO, with a moderate PPV (52.2%). Only one case of LVO was not detected by the software. Table 2 demonstrates the sensitivity, specificity, PPV, and NPV based on the data provided.

False positives accounted for 12.5% of cases (11 of 88), of which 27.3% (3 of 11) were attributed to M1 segment stenosis, e.g., Fig. 5. In one case, the M1 segment was tortuous and coursed very close to the lesser wing of sphenoid as demonstrated in Electronic Supplementary Material Fig. S1. Of the remaining seven cases, no clear cause for the false positive was identified. In one case, a partially occluded M1 was not identified by the software, for reasons unknown.

The software manufacturer, iSchemaView, specifies that the RAPID CTA software is proficient at identifying ICA and M1 occlusions. The patient cohort also included 12 medium vessel occlusions (MVO), defined as M2 or M3 segment occlusions. The RAPID CTA software correctly identified the MVO in four of 12 cases.

DISCUSSION

There are several software packages available for ASPECTS and CTA interpretation[3]. Two studies have reported that the RAPID ASPECTS outperforms neuroradiologists' interpretation[8,9]. Albers et al. studied a cohort of 65 patients, all of whom were part of a previous study (GAMES-RP) database, which included only patients with large hemisphere infarcts, with lesions of 82–300 ml on diffusion-weighted imaging (DWI). Readers were blinded to all clinical information and were not provided with access to any other imaging. The RAPID ASPECTS software had better agreement with DWI ASPECTS, when compared with readers (median error of 1 ASPECTS territory, versus 3 for readers (p<0.001). Of note, several authors, including the first author, were either shareholders, consultants, or had worked for iSchemaView, as disclosed in their paper.

Maegerlein et al. included 152 patients, of which 100 were confirmed MCA LVO cases treated with thrombectomy and 52 normal studies. RAPID ASPECTS software outperformed neuroradiologists, demonstrating substantial agreement with neuroradiologist consensus scores (κ=0.9), when compared with blinded neuroradiologist interpretation (κ=0.56 and κ=0.57); however, information that would usually be available in a real-world situation was not provided. Readers were only provided with the hemisphere affected and were not given time of onset, clinical presentation, or access to other imaging such as CTA, CTP, or previous CT examinations. RAPID software analysed the images retrospectively, i.e., they were not sent to the server at the time of scanning. Of note, Maegerlein et al. did not include patients with smaller infarcts, e.g., M2, M3, or lacunar infarcts. In addition, 32 patients could not be processed by the software and were excluded, for reasons not specified.

The present study differs in that the cohort consists of consecutive patients in the acute stroke pathway, including a larger number of normal studies and non-LVO infarcts, which may better reflect real-world clinical practice. Images were sent to RAPID in real-time, as part of the patient pathway. The only studies excluded were those that contained pathology that the AI software was not designed to process, e.g., posterior circulation infarcts, or those for which AI interpretation was not available. Readers in this study were also provided with the clinical information on the request, as well as access to previous imaging, but were not provided patient clinical notes or other details. In this context, despite the high sensitivity and NPV of RAPID ASPECTS, a large number of false positives negatively impacted the reliability of the software analysis, thereby decreasing clinicians' confidence in the algorithm.

The reason for the high number of false positive cases is not clear. There were three cases in which analysis was complicated by established MCA infarcts. In two of three cases, RAPID ASPECTS misidentified these as areas of acute infarction; however, in many instances no cause could be found, e.g., Fig. 4. It is the authors' experience that stroke clinicians often placed little reliance on the RAPID ASPECTS score in clinical decision-making due to the number of false positives.

Hoelter et al. compared three different AI/ML ASPECTS software packages Frontier, Brainomix e-ASPECTS, and RAPID[10]. They found the highest correlation between software and expert consensus reading when using the Brainomix e-ASPECTS software (*r*=0.871), followed by Frontier V2 (*r*=0.801), and RAPID (*r*=0.777). Both Brainomix e-ASPECTS and RAPID ASPECTS use ML algorithms to detect areas of early ischaemic change, while Frontier V2 uses densitometry after non-rigid registration of the ASPECTS segments[3].

A recent study demonstrated that AI/ML prediction of final infarct size is comparable to expert radiologist interpretation. In a cohort of 263 patients presenting with suspected acute ischaemic stroke, of which 83 were included, Cimflova et al. found that Brainomix had an accuracy of 75.7% in predicting follow-up ASPECTS score, compared to 79% for expert radiologists and 81.2% for cerebral blood flow (<30% on CT perfusion using RAPID software)[11]. In the present study, RAPID did not have similar success in predicting final infarct size for patients with LVO, but this is limited by the small sample size and further studies could help clarify this.

Numerous studies assessing the performance of CTA AI/ML software for the identification of LVO demonstrate sensitivities and specificities of >80%[3,12–16]. Amukotuwa et al. and Dehkharghani et al. published several studies assessing the performance of RAPID CTA software[12–14]. The largest study included 926 patients from multiple centres, including quaternary and regional hospitals[13]. In this study, the authors varied the diagnostic threshold of the algorithm, to yield a range of sensitivities and specificities for LVO detection. The high sensitivity setting demonstrated a sensitivity of 96.9% and specificity of 74.3%. The most recent study published by the same group (Dehkharghani et al.) in 2021 included 217 CTA examinations, with 109 positive for LVO[14]. Their results suggest excellent software performance with an LVO detection sensitivity of 96% and specificity of 98%. The CTA studies were chosen from a pool of 378 patients to ensure they only contained normal or LVO positive studies. Images were assessed to ensure they were technically adequate, free of artefacts that would degrade interpretation. LVO was defined as occlusion or near occlusion by a focal stenosis >80% of the vessel diameter. The majority of the authors were shareholders of, or received financial support from iSchemaView[12–14].

Seker et al. trained and evaluated the performance of Brainomix e-CTA software using a test set of 301 cases, including 160 LVOs[15]. The software had a sensitivity of 92% and specificity of 98% for proximal LVO. When compared to readers of varying levels of experience, they found that e-CTA performance was similar to less experienced readers in detecting any LVO, and comparable to experienced clinicians in detecting proximal LVO. Several authors received payment from or worked for Brainomix, as disclosed in their paper. Chatterjee et al. assessed the performance of Viz.ai using 650 consecutive CTA examinations performed for suspected acute ischaemic stroke over a 9-month period, including 195 LVOs[16]. The software had a sensitivity of 82% and specificity of 94% for LVO detection, similar to the present study; however, 41 cases were not processed due to metal artefact, inadequate contrast, motion artefact, or excess Z-spacing variability.

Similar to the studies listed above, the present findings confirm high sensitivity and specificity for detection of LVO by RAPID software. Slightly lower sensitivity in the present study, 85% versus 98% in the recent study by Dehkharghani et al. may reflect the use of a consecutive data set in the present study, including a range of studies, without pre-selection or exclusion of suboptimal studies. In addition, the present definition of LVO includes only occluded vessels and not severe stenosis >80%, which may represent other pathology. Unlike other studies, the present consecutive data set included a majority of normal cases, with only small numbers of positive LVO case, which in theory could negatively affect the sensitivity due to a small number of false negatives.

The RAPID CTA software correctly identified the MVO (M2 or M3 segment occlusions) in four of 12 cases. This is similar to the performance of Brainomix software in a recent study by Sawicki et al, in which eight of 25 M2 occlusions were correctly identified[17]. To the authors' knowledge, none of the software packages in use in UK can reliably detect MVO, but it is expected that this will be available in the not too distant future. This may be of greater clinical value due to the relative difficulty in detecting MVO as compared to LVO.

Limitations of the present study include the relatively modest sample size, and single centre, retrospective study design, which may affect the generalisability of the conclusions. Secondly, the contiguous retrospective data set included a limited number of positive ASPECTS and LVO cases, but this reflects a real-world population of patients presenting in the acute stroke pathway. Further studies with a larger sample size and multicentre design could provide more robust evidence for the use of this software package. Thirdly, 7.1% (7 of 99) of CT head studies and 13.7% (14 of 102) of CTA studies were not sent to RAPID for evaluation due to technical difficulties. Fourthly, the performance of other software packages, such as Brainomix and Viz.ai, was not assessed as these are not available at the authors' institutions.

In conclusion, RAPID CTA was robust and reliable in the detection of LVO. Although demonstrating high sensitivity and NPV, RAPID ASPECTS interpretation was associated with a high number of false positives, which decreased clinicians' confidence in the algorithm. Thus, at the authors' institution, clinicians place little reliance on the RAPID ASPECT score for clinical decision-making; however, in cases of proven LVO, RAPID ASPECTS performed well and had good correlation with neuroradiologists' blinded interpretation.

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Fig. 1. Consort diagram illustrating the patients included in the study.

Fig. 2. A 47-year-old man who presented with right-sided weakness. (a) CT head demonstrates hypoattenuation affecting the left MCA territory, involving the basal ganglia, frontal, parietal, and temporal cortex. (b) RAPID ASPECTS correctly identifies the left MCA infarct (ASPECTS score 1). (c) CTA demonstrates a left M1 occlusion, which is confirmed by RAPID CTA (d). (e) Follow-up CT head confirms a large left MCA infarct, with similar distribution to that depicted by RAPID ASPECTS and the radiologist's report.

Fig. 3. Scatter plot demonstrating the correlation between RAPID ASPECTS and mean ASPECTS of neuroradiologists 1 and 2 in patients with confirmed LVO, with 95% confidence intervals and line of best fit marked.

Fig. 4. A 55-year-old man who presented with left-sided weakness. (a) RAPID ASPECTS mis-identifies a large infarct (ASPECTS score 3) on the wrong side to the patient's symptoms. This is not apparent on the initial CT head images (not shown). (b) Follow-up CT head does not demonstrate any new infarct.

Fig. 5. An 85-year-old woman who presented with left-sided weakness. (a) CTA maximum intensity projection (MIP) demonstrates a distal right M1 stenosis. (b) RAPID CTA mis-identifies the stenotic M1 segment as an LVO.

Table 1. Sensitivity, specificity, and positive and negative predictive values for RAPID ASPECTS.

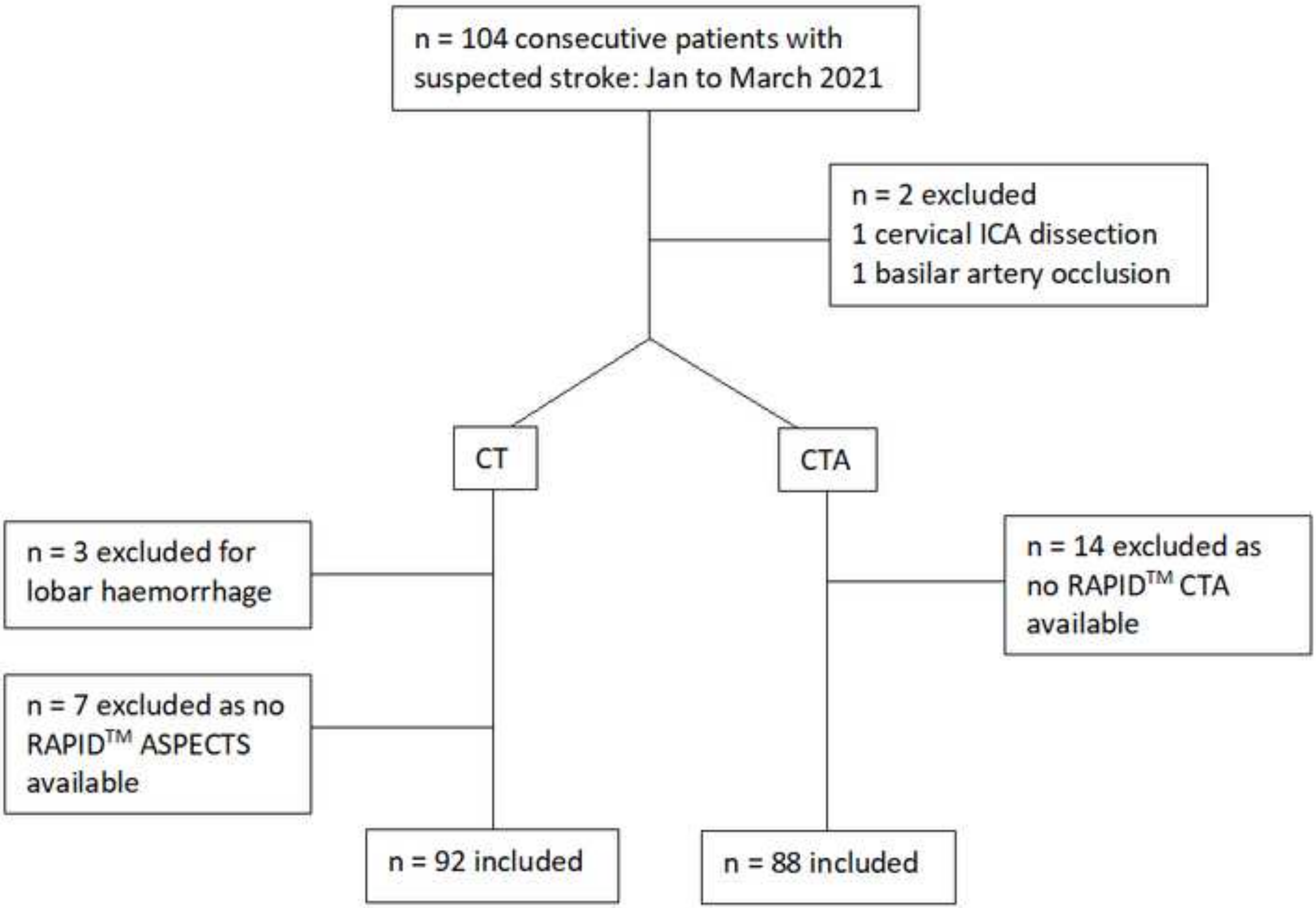
	Infarct	No infarct	
Rapid ASPECTS +	21	47	PPV 30.9%
Rapid ASPECTS –	3	21	NPV 87.5%
	Sensitivity 87.5%	Specificity 30.9%	Total=92

Infarct was determined by neuroradiologists based on the presentation CT head.

Table 2. Sensitivity, specificity, positive and negative predictive values for RAPID computed tomography angiography (CTA).

	LVO	No LVO	
Rapid CTA +	12	11	PPV 52.2%
Rapid CTA -	1	64	NPV 98.5%
	Sensitivity 92.3%	Specificity 85.3%	88

Large-vessel occlusion (LVO) was determined by neuroradiologists based on the presentation CTA.


n = 104 consecutive patients with suspected stroke: Jan to March 2021
n = 2 excluded
1 cervical ICA dissection
1 basilar artery occlusion
CT
CTA
n = 3 excluded for lobar haemorrhage
n = 7 excluded as no RAPID™ ASPECTS available
n = 14 excluded as no RAPID™ CTA available
n = 92 included
n = 88 included

Figure

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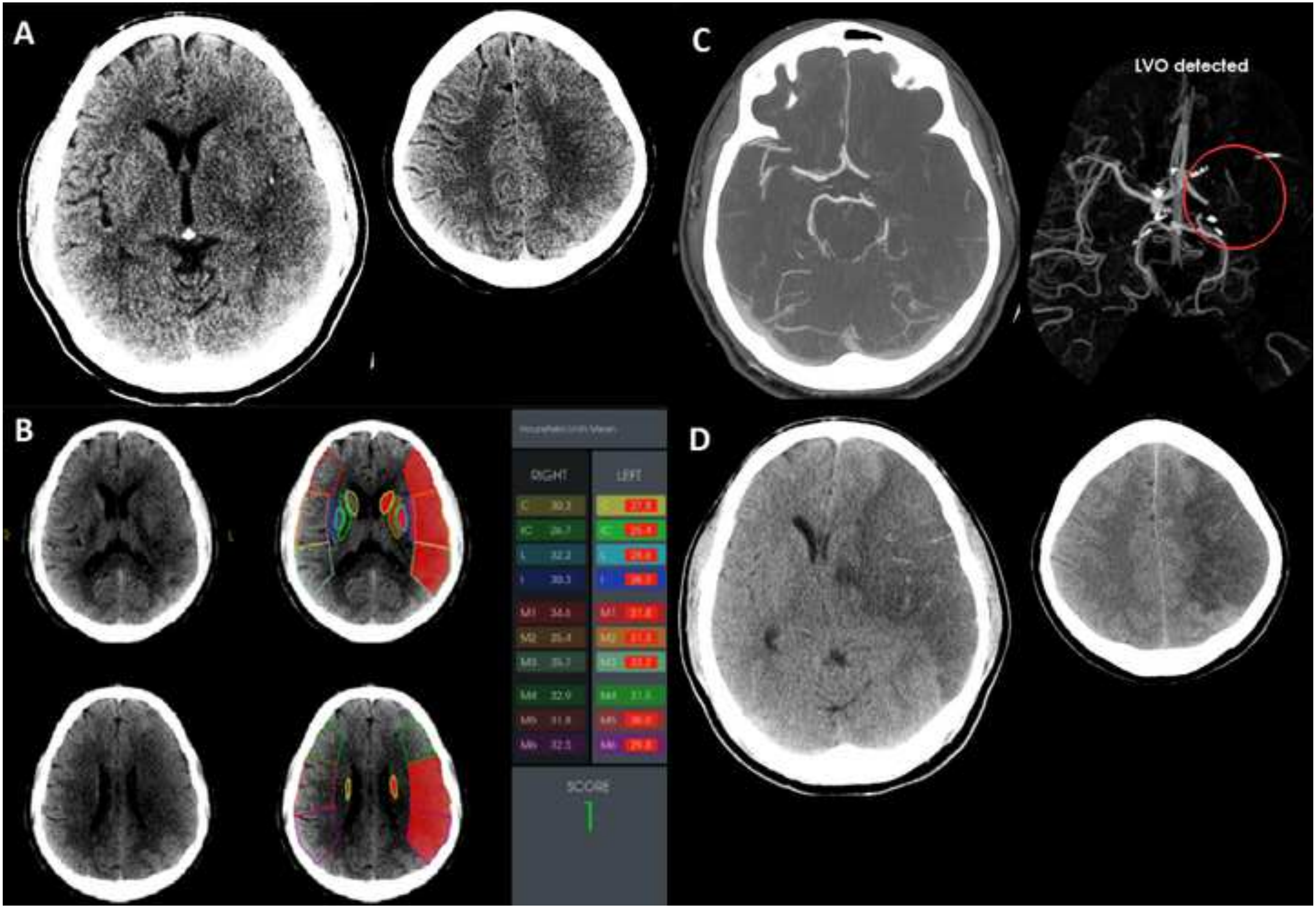

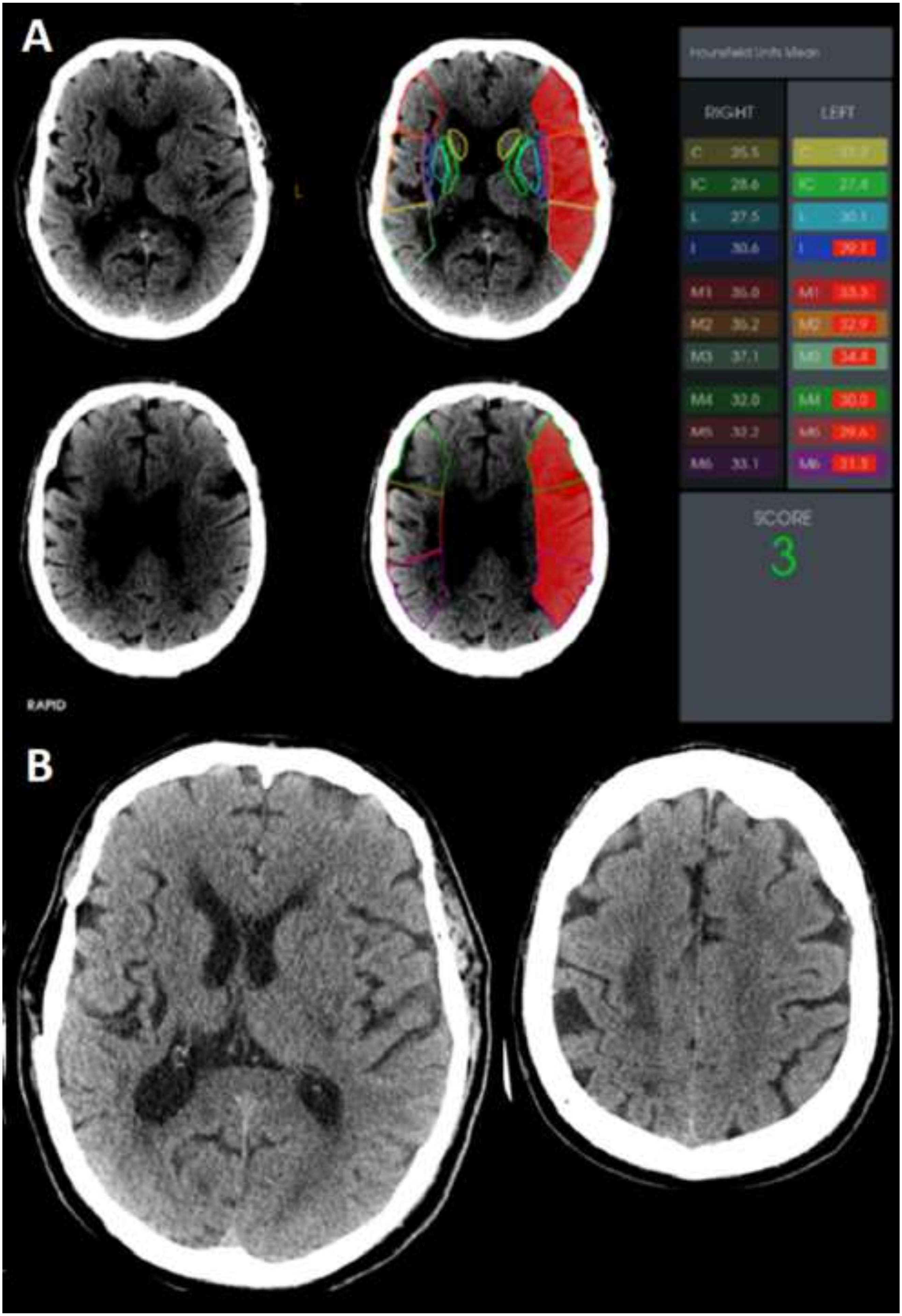
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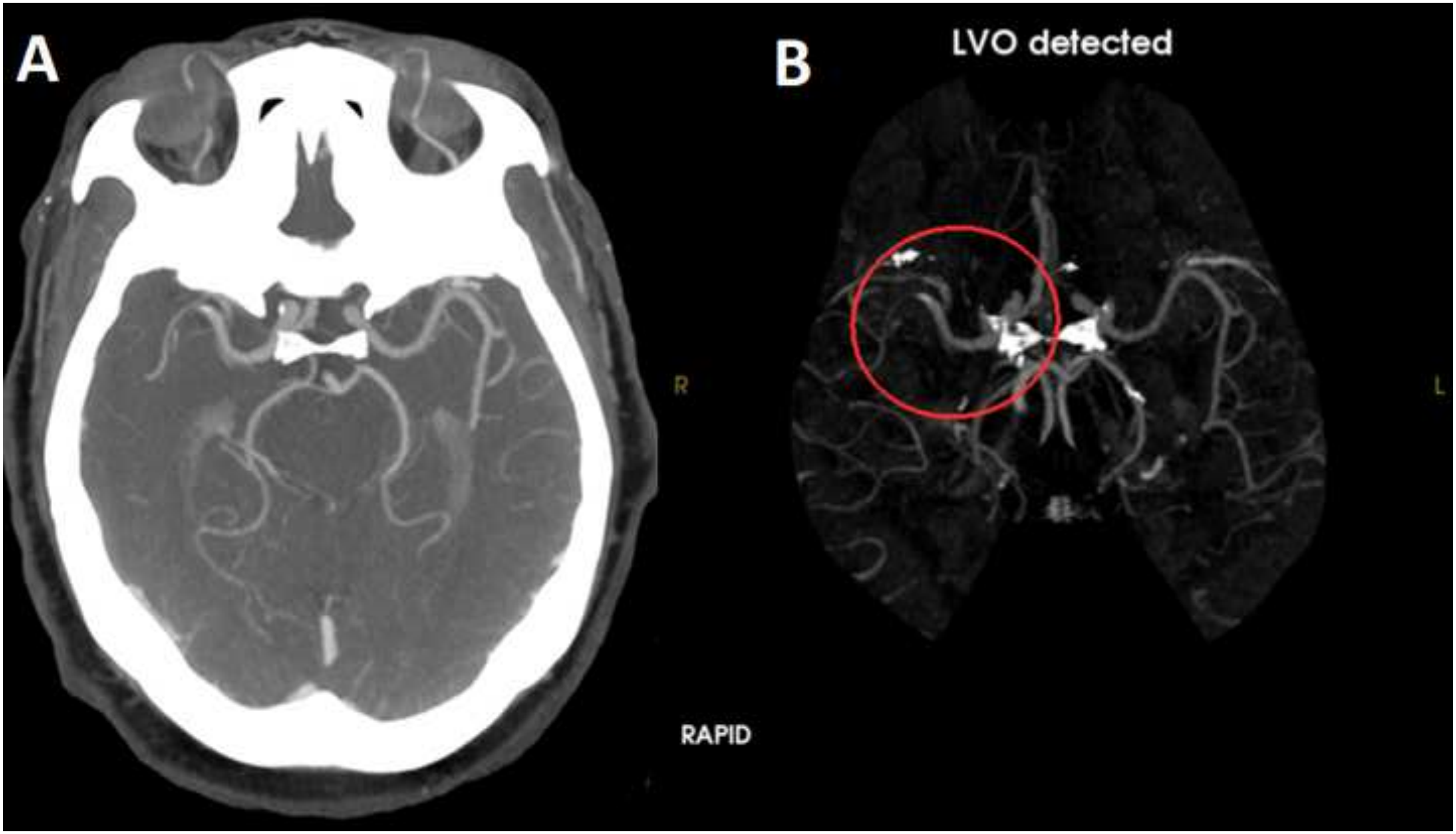
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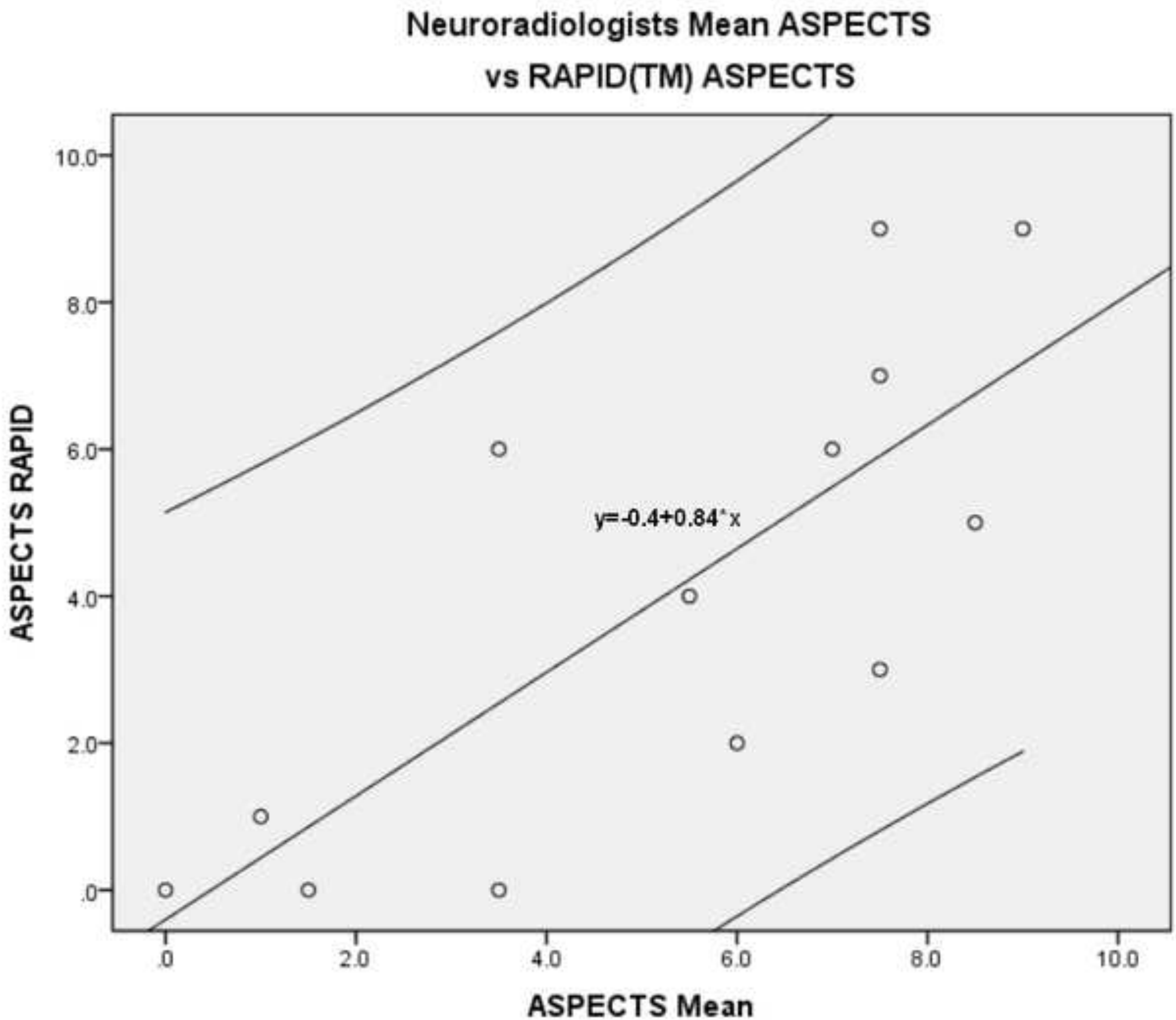
Neuroradiologists Mean ASPECTS
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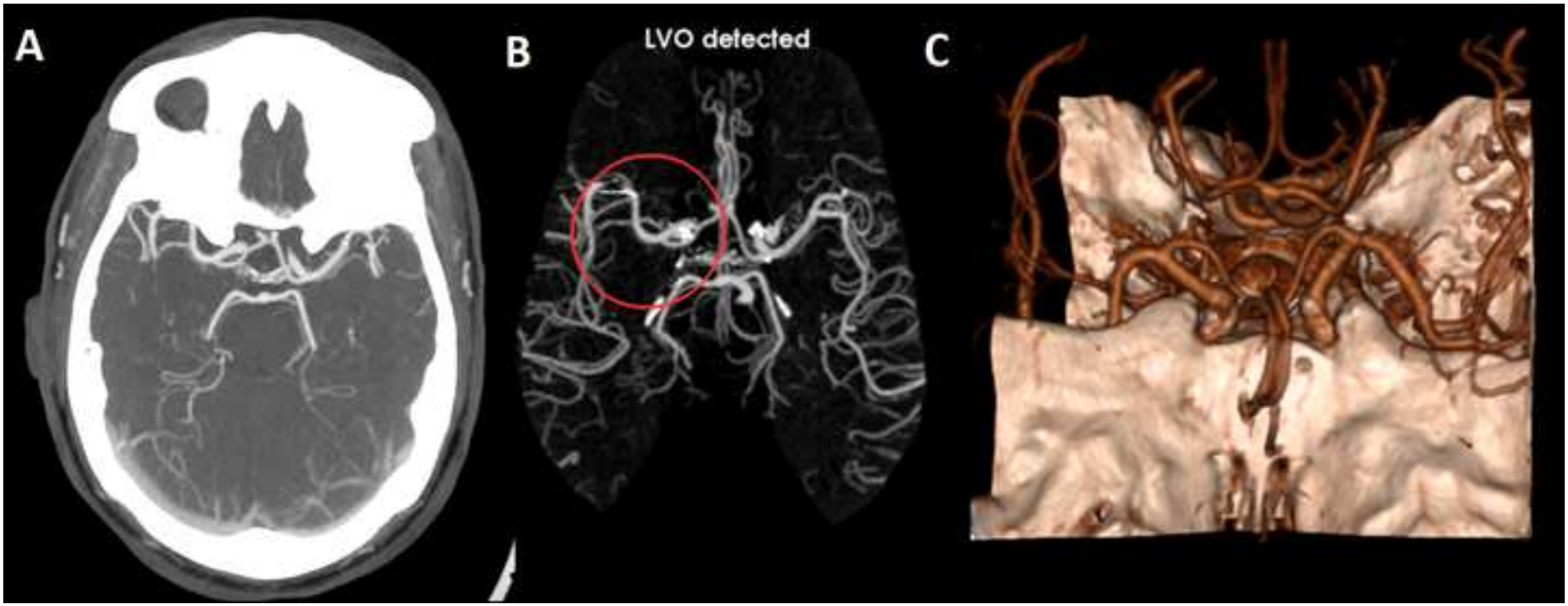
A
B
LVO detected
C

Supplementary Figure 1, 65M presenting with left sided weakness, (A) CTA maximum intensity projection demonstrates a tortuous right M1 segment with close relation to the lesser wing of sphenoid, (B) RAPID CTA mis-identifies this as an M1 occlusion. (C) 3D reconstruction of the CTA demonstrating the caudal relation of the right M1 segment to the lesser wing of sphenoid.

Declaration of interests

☐The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Thomas C Booth reports financial support was provided by Wellcome Trust.

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Highlights

- RAPID™ ASPECTS:
    - Demonstrated high sensitivity, but poor specificity for acute infarcts.
    - Is associated with a high percentage of false positives.
    - Correlates well with neuroradiologists' interpretation in cases of LVO.
- RAPID™ CTA demonstrated high sensitivity and specificity for LVO detection