

Comparison of Automated CT Perfusion Softwares in Evaluation of Acute Ischemic Stroke

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Background and Purpose: Automated imaging software is integral to decision-making in acute ischemic stroke (AIS) during extended time windows. RAPID software is the most widely used and has been validated in landmark endovascular trials. Olea software is another commercially available and FDA-approved software, but has not been studied in AIS trials. We aimed to compare the diagnostic utility and accuracy of RAPID and Olea in everyday clinical practice outside of a clinical trial. *Methods:* We analyzed prospectively-collected data from a consecutive cohort of 141 patients with suspected AIS who underwent computed tomography perfusion upon presentation followed by diffusion-weighted magnetic resonance imaging (DWI-MRI) within 24-48 hours. Core infarct was defined as the region with a relative cerebral blood flow (rCBF) less than 30% on RAPID and rCBF less than 40% on Olea (default settings). We also evaluated rCBF less than 30% on Olea to match RAPID's default setting. Infarct volume on DWI-MRI was measured using a semi-automated segmentation method. *Results:* Twenty-one patients were excluded; 14 due to poor bolus tracking and/or motion artifact, and 7 due to software failure. The software failure rate was 4.7% [6/127] with RAPID versus .78% [1/127] with Olea ($P = .12$). For the remaining 120 patients, the sensitivity and specificity for detecting an acute infarct were 40.5% and 97.6% for RAPID; 50.6% and 85.4% for Olea; and for detecting large infarcts (≥ 70 mL on DWI-MRI) 73.7% and 81.2% for RAPID; 73.7% and 68.3% for Olea. Core infarct volume on RAPID was more closely correlated with DWI-MRI infarct volume ($\rho = .64$) than Olea ($\rho = .42$). *Conclusions:* Our head-to-head comparison of these 2 commonly-used softwares in the clinical setting elucidates the pros and cons of their use to guide decision-making for AIS management in the acute setting.

Key Words: Stroke—computed tomography—perfusion imaging—RAPID—Olea
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Introduction

Recent clinical trials have demonstrated that endovascular intervention is an effective treatment for acute ischemic stroke (AIS) due to large vessel occlusion (LVO),¹⁻⁷

and that imaging-based patient selection dramatically improves clinical outcomes.¹⁻³ Because computed tomography (CT) is readily available in emergency departments,

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computed tomography perfusion (CTP) is widely used to detect the ischemic core and tissue at risk of infarction, that is, the ischemic penumbra, to guide therapeutic decision-making and the selection of appropriate patients with AIS and LVO who are most likely to benefit from endovascular therapy during the extended time window.

Several software packages have been developed to automatically identify the ischemic core and penumbra. The utility of the RAPID software (iSchemaView Inc, Menlo Park, CA) was validated in several landmark interventional trials,¹⁻³ and it has been adopted by more than 1000 hospitals worldwide (<http://www.i-rapid.com/home>). The Olea software (Olea Medical Solutions, La Ciotat, France) is another commercially available and FDA-approved automated software that is utilized in more than 200 centers (<https://www.olea-medical.com/en/>). To our knowledge, the Olea software has not been formally tested in AIS trials. There is a paucity of information regarding the diagnostic utility and accuracy of these commonly-used software packages in everyday clinical practice outside the framework of a clinical trial. Therefore, we sought to simultaneously investigate the diagnostic utility and accuracy of the RAPID and Olea CTP software packages in diagnosing AIS in a cohort of patients with suspected AIS.

Methods

Study Design and Participants

This was a single center, retrospective, and observational study. We identified all suspected stroke cases that presented within 24 hours of symptom onset and required “code stroke” activation between August 2017 and July 2018. Per our protocol, all these cases underwent CT, CTP, and CT angiography (unless there were contraindications to the use of iodine contrast). We excluded cases that did not undergo CTP or subsequent diffusion-weighted magnetic resonance imaging (DWI-MRI) during hospitalization. Because the Olea software automatically processes the results for only one side of the brain, while RAPID can simultaneously process results for both sides, we also excluded cases with bilateral infarcts on RAPID to assure uniformity of the automated results.

We retrieved clinical and radiological data, and used perfusion data to perform simultaneous measurements of the infarct core and hypoperfused tissue using both RAPID and Olea imaging softwares. Eligible patients were given intravenous tPA and/or thrombectomy according to the guideline for acute stroke management.⁸ CTP images were used for clinical decision-making for ruling out stroke mimics in conjunction with clinical manifestations⁹ and patient selection for thrombectomy. A combination of clinical judgment, exam findings, laboratory tests, and CTP images were used to rule out stroke in favor of a stroke mimic. CTP was used to support the possibility of a stroke versus a stroke mimic in situations where the clinical diagnosis of stroke was suspect on clinical grounds. For example, the lack of a visible perfusion

deficit in patients with a suspected stroke mimic was interpreted as a potentially supportive evidence for a nonstroke diagnosis, and later confirmed with DWI MRI. Similarly, the lack of a perfusion deficit (and LVO on CT angiography) in patients with stroke-like symptoms and hypoglycemia was used to support the diagnosis of a stroke mimic due to a metabolic derangement. In other instances, hyperperfusion (not hypoperfusion) on CTP was used to support the diagnosis of a seizure resulting in postictal paralysis. Successful recanalization was defined as a post-thrombectomy modified Treatment in Cerebral Ischemia Scale (mTICI) score of 2b-3 on digital subtraction angiography.¹⁰ The study was approved by the institutional review board and ethics committee at Beth Israel Deaconess Medical Center with a waiver of informed consent.

CTP Imaging Acquisition

CTP was performed using a 64-slice CT scanner (Light-Speed VCT, GE Healthcare). Patients were scanned at a collimation of $64 \times .625$, pitch of .52, rotation time of .5 seconds, matrix of 512×512 , thickness of 5 mm, and 80 kV. CTP images were obtained after the injection of 40 mL of ioversol (Optiray 320, Covidien) at 5 mL/s via an antecubital vein.

Automated Software on Computed Tomography Perfusion

RAPID (iSchemaView Inc, Menlo Park, CA) defines infarct core as regions with a relative cerebral blood flow (rCBF) less than 30% of that in normal tissue, and hypoperfused tissue as that with Tmax greater than 6 seconds.

Olea Sphere 3.0.12 (Olea Medical Solutions, La Ciotat, France) recommends 2 thresholds for rCBF: (1) rCBF less than 30% and Tmax greater than 2 seconds, which matches RAPID¹¹; and (2) rCBF less than 40% and Tmax greater than 2 seconds which is considered the default and most accurate setting for detecting an acute infarct.¹² Tmax greater than 2 seconds is used to rule out an old infarct. The hypoperfused tissue is defined as that with Tmax greater than 6 seconds.

MRI Infarct Volume Measurement

An experienced neurologist (Y.X.) measured the DWI-MRI infarct volume in the whole brain using a semiautomated segmentation method with the ANALYZE software version 11.0 (AnalyzeDirect, Overland Park, KS).¹³ Fifteen cases were randomly selected to test intrarater and inter-rater reliability (Y. X. and a junior neuroradiologist C.H.), which yielded .996 (.990-.999) and .982 (.947-.994), respectively.

Spatial Match between CTP and MRI

Two raters (Y.X. and C.H.) visually rated infarct regions with simultaneous review of RAPID and Olea summary output and DWI map, and came to a consensus of whether the

location of infarcts detected on CTP overlaps with the infarct regions seen on DWI-MRI. We were unable to coregister RAPID or Olea images with DWI images because only the summary outputs of RAPID/Olea with core infarct delineation were stored in our PACS system. Spatial match between CTP and DWI was defined as an overlap of the ischemic core on CTP with at least one of the acute infarct regions on DWI (size of CTP core \leq DWI infarct for the same location). Infarcts detected on CTP that were larger than corresponding DWI infarcts or are in a completely different region than acute infarcts seen on DWI were considered to be not spatially matched.

Statistical Analysis

Continuous variables were described as mean \pm SD for normally distributed data and median (interquartile range) for skewed data. Data normality was tested by 1-sample K-S test. Chi-square tests and Fisher's exact tests were used to compare the categorical variables. Agreement of RAPID and Olea against MRI on infarct identification was evaluated by Kappa value, with 0-.20 as slight, .21-.40 as fair, .41-.60 as moderate, .61-.80 as substantial, and .81-1 as almost perfect agreement.¹⁴ Diagnostic values including sensitivity, specificity, positive predictive value, and negative predictive value were provided. Spearman correlation tests (for skewed data) and Pearson correlation tests (for normally distributed data) were used to assess the correlation of DWI-MRI infarct volume with RAPID and Olea volumes. In addition, Bland-Altman plots were utilized to assess the agreement of CTP core volumes with DWI-MRI infarct volume. Moreover, the volumetric difference between CTP and DWI-MRI infarct volume was defined as DWI-MRI infarct volume minus CTP infarct volume for each case. Wilcoxon signed rank test (for skewed data) and paired sample *t* test (for normally distributed data) were utilized to compare the volumetric differences.

Sensitivity tests were performed in subgroups. For the neurointerventional cases with successful recanalization, we tested the correlation between CTP core volumes and DWI-MRI infarct volume. With regards to patients without tPA or thrombectomy, Tmax greater than 6 and combination of core volume + Tmax greater than 6 seconds were previously reported to be highly correlated with 24-hour MRI infarct volume.¹⁵ Thus, the correlations of DWI-MRI infarct volume with Tmax greater than 6 seconds and combination of core volume + Tmax greater than 6 seconds were evaluated in patients without tPA or thrombectomy. Statistical analysis was performed using the SPSS version 22 software package (SPSS Inc, Chicago, IL).

Results

Patient Characteristics

A total of 141 cases met our eligibility criteria; 14 (9.9%) of whom were excluded due to severe motion artifact and/or poor bolus tracking time. Of the remaining 127 cases,

RAPID failed to provide any results in 6 (4.7%) and Olea failed in 1 (.78%) ($P = .12$). The reasons of RAPID/Olea failures were related to undetected arterial input function or venous output function, and software instability. Therefore, a total of 120 cases were included in study analyses. Poor arterial input and venous output functions were noted in 7 of 120 (5.8%) cases on RAPID versus 15 (12.5%) on Olea ($P = .59$). No case with poor arterial input/venous output overlapped on RAPID and Olea. Table 1 shows the clinical characteristics of the included patients. Eighty-six (71.6%) patients had a final diagnosis of stroke/TIA; of whom 45 (52.3%) were treated with intravenous tPA and/

Table 1. Clinical characteristics of the subjects

	Subjects (N = 120)
Age (y)	69.5 \pm 15.2
Male	42 (35%)
Coronary artery disease	15 (12.5%)
Atrial fibrillation	23 (19.2%)
Hypertension	78 (65.0%)
Diabetes mellitus	45 (37.5%)
Hyperlipidemia	36 (30.0%)
Coronary heart failure	6 (5.0%)
Carotid moderate to severe stenosis	
Contralateral only	5 (4.2%)
Ipsilateral only	11 (9.2%)
Both sides	1 (.8%)
NIHSS at admission	8 (3-17)
<i>Time intervals</i>	
Stroke symptom onset to CTP time, hours	5.2 (2.5-11.2)
Stroke symptom onset to MRI time, hours	30.5 (21.5-46.8)
CTP-to-MRI time, median (IQR), hours	23.5 (12.7-37.3)
<i>Diagnosis</i>	
Stroke/TIA	86 (71.6%)
Stroke mimics	33 (27.5%)
Other conditions	1 (.8%)
<i>Treatment methods^a</i>	
Intravenous tPA alone	14 (16.3%)
Thrombectomy alone	18 (20.9%)
Intravenous tPA+thrombectomy	13 (15.1%)
Occlusion site for thrombectomy cases ^b	
Middle cerebral artery	23 (74.2%)
Internal carotid artery	8 (25.8%)
mTICI for thrombectomy cases ^b	
0-2a	3 (9.7%)
2b-3	28 (90.3%)

Data were presented as mean \pm SD or median (interquartile range) for continuous variables and n (%) for categorical variables. CTP: computed tomography perfusion; Abbreviations: MRI: magnetic resonance imaging; mTICI: Modified Treatment in Cerebral Ischemia Scale.

^aProportion was calculated in patients with stroke/TIA (N = 86).

^bData were analyzed in thrombectomy cases (N = 31).

or thrombectomy. Forty-six patients with AIS had LVO on CT angiography. Occlusion sites were internal carotid artery (26.2% [12/46]), middle cerebral artery (M1 65.2% [30/46], M2 2.2% [1/46], M3 4.3% [2/46]), and posterior cerebral artery (2.2% [1/46]). Thirty-one of these 46 patients underwent thrombectomy. The median (interquartile range) of CTP to recanalization time was 1.2 (.9-1.9) hours. Stroke mimics were listed in eTable 1 in the supplement.

Diagnostic Values for an Acute Infarct

Seventy-nine cases (65.8%) had acute infarcts seen on DWI-MRI. Table 2 shows the diagnostic values of CTP for detection of an acute infarct. Overall, RAPID had the best sensitivity and specificity (Youden index = .38), followed by Olea (rCBF < 30%) (Youden index = .36), then Olea (rCBF < 40%) (Youden index = .09). Positive and negative predictive values were 97.0% and 46.0% for RAPID, 87.0% and 47.3% for Olea (rCBF < 30%), and 68.3% and 50.0% for Olea (rCBF < 40%).

The accuracy of diagnosing acute infarct on CTP and MRI are shown in eTable 2 in the Supplement. The agreement of DWI-MRI with RAPID and Olea on acute infarct identification was as follows: RAPID versus MRI: Kappa = .30; Olea [rCBF < 30%] versus MRI: Kappa = .30; Olea [rCBF < 40%] versus MRI: Kappa = .11. eTable 3 in the Supplement summarizes the comparison of CTP infarct volumes with RAPID and Olea for cases in which a DWI-MRI infarct and an identifiable core on CTP were identified. It shows that RAPID core volume were larger than Olea (rCBF <

30%) core volume ($P < .001$), but comparable with Olea (rCBF < 40%) core volume ($P = .50$). The critical hypoperfusion volumes were not different using these 2 softwares ($P = .70$ and $.49$).

In cases with DWI-MRI infarct but without identifiable core on CTP ($n = 47$ for RAPID, 39 for Olea [rCBF < 30%] and 8 for Olea [rCBF < 40%]), the proportion of cases with Tmax greater than 6 seconds was 71.2% (33/47) for RAPID, 89.7% (35/39) for Olea (rCBF < 30%) and 87.5% (7/8) for Olea (rCBF < 40%).

Regarding the ability to detect large infarcts (DWI-MRI infarct volume ≥ 70 mL), RAPID had a better sum of sensitivity and specificity (Youden index = .55) and moderate agreement with MRI (Kappa = .42) than Olea (rCBF < 30%: Youden index = .42, Kappa = .27; rCBF < 40%: Youden index = .09, Kappa = .03) (Table 3). In the subgroup of patients with DWI-MRI infarct volume greater than or equal to 70 mL, Tmax greater than 6 seconds (mean \pm SD) on RAPID was 168.6 ± 97.6 mL versus 176.4 ± 113.4 mL on both Olea rCBF < 30% and rCBF < 40% ($P = .65$).

Volumetric Correlation of DWI-MRI Infarct Volume with RAPID and Olea CTP Volumes

Table 4 shows the correlation between CTP infarct volumes and DWI-MRI infarct volume in patients with DWI-MRI infarcts. The median (interquartile range) DWI-MRI infarct volume was 20.4 (1.9-65.7) mL. Overall, RAPID core volumes were more closely correlated with DWI-MRI infarct volume than those of Olea in all DWI-MRI infarct cases and in thrombectomy cases with

Table 2. Diagnostic values for acute infarct detection

	Sensitivity	Specificity	PPV	NPV
RAPID (rCBF < 30%)	40.5%	97.6%	97.0%	46.0%
Olea (rCBF < 30%)	50.6%	85.4%	87.0%	47.3%
Olea (rCBF < 40%) ^a	89.9%	19.5%	68.3%	50.0%

Abbreviations: NPV: negative predictive value; PPV: positive predictive value.

^aOlea default setting.

Table 3. The accuracy of diagnosing acute large infarct on CTP and MRI

Baseline CTP	Follow-up DWI-MRI infarct volume ≥ 70 mL		Kappa	P
	Yes N = 19	No N = 101		
RAPID (rCBF < 30%)				
Ischemic core	14 (73.7%)	19 (18.8%)	.42	<.001
No ischemic core	5 (26.3%)	82 (81.2%)		
Olea (rCBF < 30%)				
Ischemic core	14 (73.7%)	32 (31.7%)	.27	.001
No ischemic core	5 (26.3%)	69 (68.3%)		
Olea (rCBF < 40%)				
Ischemic core	18 (94.7%)	86 (85.1%)	.03	.26
No ischemic core	1 (5.3%)	15 (14.9%)		

Table 4. The correlation of MRI infarct volume with RAPID and Olea CTP parameters in patients with MRI infarct

CTP	RAPID/Olea volumes	MRI infarct volume	Rho	P
Overall cases (N = 79)				
RAPID core volume	0 (0-28.0)	20.4 (1.9-65.7)	.64	<.001
Olea core volume (rCBF<30%)	.5 (0-5.0)		.42	<.001
Olea core volume (rCBF<40%)	15.2 (3.2-28.4)		.33	.003
Neurointerventional cases with mTICI 2b-3 (N = 28)				
RAPID core volume	10.0 (0-39.5)	19.5 (6.7-96.3)	.53	.004
Olea core volume (rCBF<30%)	.9 (0-6.4)		.41	.03
Olea core volume (rCBF<40%)	15.7 (4.2-30.0)		.39	.04

Data were presented as mean ± SD or median (interquartile range) for continuous variables, unit for volume was mL.

successful recanalization. RAPID Tmax greater than 6 seconds and combination of core+Tmax greater than 6 seconds volumes are numerically higher than those of Olea volumes in patients without tPA or thrombectomy (eTable 4 in the supplement). Figure 1 shows that RAPID had better agreement than Olea by Bland-Altman plot in all DWI-MRI infarct cases. Similar results were noted in neurointerventional cases (eFig 1 in the supplement). eTable 5 in the supplement shows the absolute differences between DWI-MRI infarct volume and volumes on CTP software packages. In all DWI-MRI infarct cases and thrombectomy cases with successful recanalization, RAPID had closer core volume with MRI infarct volume than Olea using rCBF less than 30%. Olea using rCBF less than 40% had the highest overestimation rate (36.7% [29/79] for all DWI-MRI infarct cases, and 42.9% [12/28] for thrombectomy cases with successful recanalization). In patients without tPA or thrombectomy, Tmax greater than 6 seconds and combination of core volume + Tmax greater than 6 seconds overestimated infarct volume with both RAPID and Olea softwares; Olea greater than RAPID.

Spatial Match between CTP and MRI

An overlap between the location of infarcts detected on CTP and DWI-MRI was present in 27 of 79 (34.1%) cases with RAPID versus 22 of 79 (27.8%) with Olea (rCBF <

30%) (P = .39) and 13 of 79 (16.5%) with Olea (rCBF < 40%) (P = .01). In spatially-matched cases on each CTP software, RAPID core volume significantly correlated with DWI-MRI infarct volume (r = .57, P = .002), followed by Olea (rCBF < 40%) (r = .51, P = .07). There was no significant correlation seen with Olea (rCBF < 30%) (r = .18, P = .44) (eTable 6 in the Supplement).

Discussion

We report the advantages and limitations of 2 commonly used CTP software packages in the clinical setting. In our cohort, the main drawback of RAPID was its numerically higher failure rate to detect ischemic brain regions as compared to Olea. The RAPID software had moderate sensitivity and high specificity for core infarct and moderate volumetric and spatial agreement, which is in line with previous studies.^{16,17} The RAPID software, however, had better accuracy for diagnosing infarcts greater than or equal to 70 mL as well as a closer volumetric correlation and lesser volume differences with DWI-MRI infarct volume than Olea, particularly in spatially-matched cases.

Our finding that RAPID was better in detecting large infarcts greater than or equal to 70 mL may have important practice implications. Overall, RAPID performed better than Olea (rCBF < 40%). However, Olea (rCBF < 30%) was more comparable to RAPID. However, Olea (rCBF <

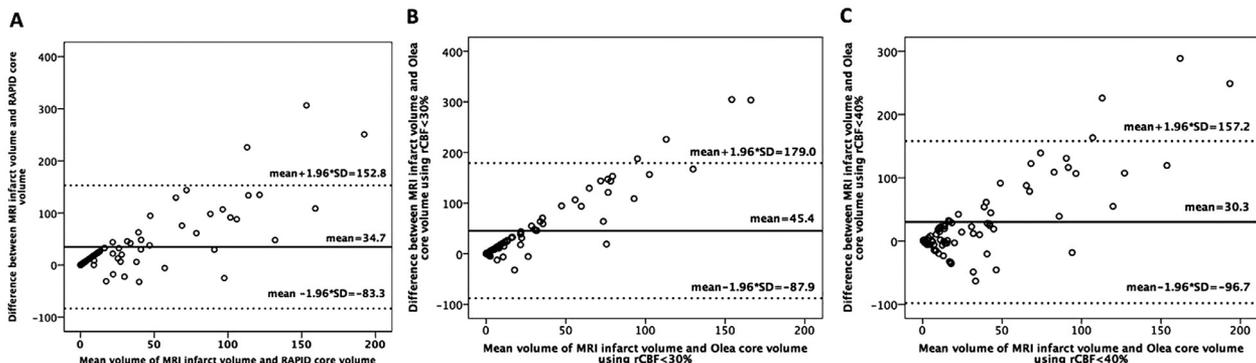


Figure 1. Agreement between MRI infarct volume and CTP core volume. Bland-Altman plot of the differences between MRI infarct volume and (A) RAPID core volume, (B) Olea core volume using rCBF < 30% and (C) Olea core volume using rCBF < 40%, respectively. Overall, the RAPID provides the narrowest limits of agreement (-83.3 mL to 152.8 mL).

30%) may underestimate infarct core volume and caution is required when using Olea (rCBF < 30%) to make therapeutic decisions in borderline cases, such as a core infarct ~ 60 mL. Large infarcts are considered to be a marker for poor clinical outcome, a risk factor for hemorrhagic transformation, and have been used as an exclusion criterion in some endovascular stroke trials,^{1,2} although this has been recently debated.¹⁸ The ability of RAPID to better identify large infarcts compared to Olea may support its use over Olea for decision-making in potential thrombectomy cases.

The default setting of core infarct for Olea Sphere 3.0.12 is rCBF less than 40% and Tmax greater than 2 seconds.¹² A previous study recommended using the default setting for comparison between different packages against MRI.¹⁹ However, in our cohort, the rCBF less than 30% threshold performed better than rCBF less than 40% with the Olea software for acute infarct detection with overall closer volumetric correlation with MRI. Although the correlation with DWI-MRI infarct in spatially-matched cases was higher in Olea (rCBF < 40%) than Olea (rCBF < 30%), the frequency of spatially-matched cases was higher with Olea (rCBF < 30%). These results suggest that the optimal threshold for defining infarct core on Olea using receiver operator curve analysis with several different thresholds warrants further investigation. Based on our results, the use of rCBF less than 30% instead on less than 40% may be recommended to define core infarct on Olea. This requires further confirmation in a larger cohort of patients. The use of Tmax greater than 2 seconds as a threshold to rule out an old infarct is an additional feature in Olea. However, it did not result in improved correlation between Olea core volume and DWI-MRI acute infarct volume.

Our study has limitations. First, the Olea and RAPID all used the popular singular value deconvolution postprocessing method, which is more sensitive to noise. A recent study reported that Bayesian postprocessing increased accuracy and limited availability in CTP estimation of infarct core when compared with the singular value deconvolution postprocessing.¹¹ Further studies are warranted using the Bayesian postprocessing method to compare these software packages. Second, the sample size of patients undergoing thrombectomy is small, and the time intervals between CTP and MRI were not standardized due to the retrospective nature of our study. However, RAPID and Olea processing was performed on the same CTP source images. Third, we only included cases with unilateral core on CTP in this study. Therefore, the comparison of these 2 softwares in patients with bilateral cores on CTP needs further investigation. Although our data regarding correlation between CTP and DWI-MRI infarct volumes should be interpreted with caution because we did not have recanalization data for all patients, we found high correlation of Tmax greater than 6 seconds volume and the combination of core +Tmax greater than 6 seconds volume with MRI infarct volume in patients who did not receive tPA or undergo thrombectomy, which

corresponds with recent findings by Rao et al¹⁵ Fourth, although automated softwares were not developed to evaluate TIA or to confirm acute infarctions, we looked at their diagnostic value for acute infarct detection because CTP is used in clinical practice not only to assess penumbral tissue and candidacy for thrombectomy in the extended time window, but also to confirm a stroke diagnosis and to potentially identify stroke mimics.⁹ We intentionally did not want to limit our analysis to thrombectomy cases given the broader use of CTP in clinical practice. Furthermore, we directly compared 2 softwares for CTP at baseline, the trend for infarct growth would be similar for the 2 softwares' measures regardless the treatment of the patient. Fifth, spatial coregistration would be possible with the use of DICOM images. Unfortunately, the commercial versions of the RAPID and Olea softwares (but not research versions) provide the summarized images with core/hypoperfused lesion volume. Therefore, we are not able to retrieve the original DICOM image with contour of the core and hypoperfused area. As a result, we had to rely on visual assessments for both softwares in our study. Sixth, one of the limitations of the retrospective nature of our study is the inconsistent timing and availability of long-term functional outcome data and small number of patients with large vessel occlusion undergoing thrombectomy with successful recanalization. To address this limitation, we are currently evaluating the relationship between RAPID versus Olea imaging data and 90-day mRS in a prospective cohort of ischemic stroke patients with LVO who undergo thrombectomy and achieve successful recanalization. Last, our study only examined Olea & RAPID, but not other emerging softwares.

Conclusion

Our direct comparisons of the diagnostic utility and accuracy of these 2 commonly-used softwares elucidate the pros and cons of each software and their use to guide decision-making in AIS management during the acute setting in everyday clinical setting. Further prospective studies in larger number of patients undergoing thrombectomy are needed to further validate our findings.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Dr. Xiong had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Selim and Bhadelia were joint senior authors. Concept and design: Selim, Bhadelia and Xiong. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Xiong. Critical revision of the manuscript for important intellectual

content: All authors. Statistical analysis: Xiong. Administrative, technical, or material support: Hackney and Bhadelia; Supervision: Selim and Bhadelia.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.jstrokecerebrovasdis.2019.104392](https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.104392).

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