Stroke

CLINICAL AND POPULATION SCIENCES

Computed Tomography Perfusion–Based Machine Learning Model Better Predicts Follow-Up Infarction in Patients With Acute Ischemic Stroke

Hulin Kuang, PhD; Wu Qiu, PhD; Anna M. Boers, PhD; Scott Brown, PhD; Keith Muir, MD; Charles B.L.M. Majoie, MD; Diederik W.J. Dippel, MD; Phil White, MD; Jonathan Epstein, MD; Peter J. Mitchell, MBBS; Antoni Dávalos, MD; Serge Bracard, MD; Bruce Campbell, PhD; Jeffrey L. Saver, MD; Tudor G. Jovin, MD; Marta Rubiera, MD; Alexander V. Khaw, MD; Jai J. Shankar, MD; Enrico Fainardi, MD; Michael D. Hill, MD; Andrew M. Demchuk, MD; Mayank Goyal, MD; Bijoy K. Menon, MD; for the PRoveIT and HERMES Collaborators

BACKGROUND AND PURPOSE: Prediction of infarct extent among patients with acute ischemic stroke using computed tomography perfusion is defined by predefined discrete computed tomography perfusion thresholds. Our objective is to develop a threshold-free computed tomography perfusion–based machine learning (ML) model to predict follow-up infarct in patients with acute ischemic stroke.

METHODS: Sixty-eight patients from the PRoveIT study (Measuring Collaterals With Multi-Phase CT Angiography in Patients With Ischemic Stroke) were used to derive a ML model using random forest to predict follow-up infarction voxel by voxel, and 137 patients from the HERMES study (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) were used to test the derived ML model. Average map, T_{max}, cerebral blood flow, cerebral blood volume, and time variables including stroke onset-to-imaging and imaging-to-reperfusion time, were used as features to train the ML model. Spatial and volumetric agreement between the ML model predicted follow-up infarct and actual follow-up infarct were assessed. Relative cerebral blood flow <0.3 threshold using RAPID software and time-dependent T_{max} thresholds were compared with the ML model.

RESULTS: In the test cohort (137 patients), median follow-up infarct volume predicted by the ML model was 30.9 mL (interquartile range, 16.4–54.3 mL), compared with a median 29.6 mL (interquartile range, 11.1–70.9 mL) of actual follow-up infarct volume. The Pearson correlation coefficient between 2 measurements was 0.80 (95% CI, 0.74–0.86, $P<0.001$) while the volumetric difference was −3.2 mL (interquartile range, −16.7 to 6.1 mL). Volumetric difference with the ML model was smaller versus the relative cerebral blood flow <0.3 threshold and the time-dependent T_{max} threshold ($P<0.001$).

CONCLUSIONS: A ML using computed tomography perfusion data and time estimates follow-up infarction in patients with acute ischemic stroke better than current methods.

GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: acute ischemic stroke ■ computed tomographic perfusion ■ infarction ■ machine learning

Computed tomographic perfusion (CTP) has been used to estimate ischemic core and penumbra in patients with acute ischemic stroke (AIS), thereby assisting treatment decision making.[1] Current CTP thresholds (T_{max}, cerebral blood flow [CBF], and cerebral blood volume) are not informed by time from stroke onset-to-imaging and to reperfusion.[2–5] This is problematic as infarcts grow over time; conceptually, CTP thresholds that predict ischemic

Correspondence to: Wu Qiu, PhD, 1079, 29th St, Calgary, Canada T2N2T9, Email qiu.wu.ch@gmail.com or Bijoy K. Menon, MD, 1079, 29th St, Calgary, Canada T2N2T9, Email docbijoymenon@gmail.com

This manuscript was sent to Kazunori Toyoda, Consulting Editor, for review by expert referees, editorial decision, and final disposition.

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.120.030092.

For Sources of Funding and Disclosures, see page 230.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
CBF	cerebral blood flow
CTP	computed tomography perfusion
DWI	diffusion-weighted imaging
IQR	interquartile range
ML	machine learning
NCCT	noncontrast computed tomography
rCBF	relative cerebral blood flow
RF	random forest

core should likely be time variant and dependent on the patient's unique physiology, for example, their collateral status or propensity of brain tissue ischemia.[6,7] Furthermore, the predictive power of CTP thresholds could potentially be enhanced by using multiple parameters that have different physiological meaning, for example, T_{max}, CBF, cerebral blood volume. Finally, the relationship between severity of ischemia and the CTP parameters are likely nonlinear, whereas optimal thresholds from a single CTP parameter are conventionally derived using statistical models that assume linearity.[6,7]

To integrate the various effects of multiple CTP parameters and time from stroke onset-to-imaging and reperfusion into ischemic core prediction at a voxel level, we derive and then validate a machine learning (ML) model having multiple CTP parameters and time. We hypothesize that the developed ML model using random forest is more accurate and reliable than a commonly used single CTP parameter in estimating follow-up infarct.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Selection

We included patients with AIS with anterior circulation occlusions from the PRoveIT study (Measuring Collaterals With Multi-Phase CT Angiography in Patients With Ischemic Stroke)[8] and the HERMES collaboration.[9] Both studies had ethics approval from local ethics review boards. Sixty-eight patients from the PRoveIT study used to derive previously published time-based CTP thresholds were used to derive and validate the proposed ML model.[7] One hundred thirty-seven patients from the HERMES collaboration used to confirm time-based CTP thresholds for prediction of follow-up infarction were used to test the derived ML model independently.[10] All included patients had (1) CTP imaging at baseline with at least 8 cm *z*-axis coverage; (2) underwent endovascular thrombectomy; (3) had reperfusion assessed on conventional angiography after the endovascular treatment using the modified Thrombolysis in Cerebral Infarction)[11]; (4) had stroke symptom onset-to-imaging and imaging-to-reperfusion time recorded; and (5) had 24-hour follow-up noncontrast computed tomography (NCCT) or magnetic resonance diffusion-weighted imaging (DWI) imaging.

CTP Imaging

Each CTP study was processed by commercially available delay-insensitive deconvolution software (CT Perfusion 4D, GE Healthcare). Absolute maps of CBF (mL·min^{-1}·100 g^{-1}), cerebral blood volume (mL·100 g^{-1}), time to the maximum of the impulse residue function (IRF) (T_{max}: seconds), were calculated using CT Perfusion 4D. In-plane patient motion was corrected before processing, and the images with extreme motion at specific time points were manually removed.[7] Average maps were created by averaging the dynamic CTP source images.

Image Analysis

For the derivation cohort of 68 patients from the PRoveIT study, follow-up infarct was manually delineated by consensus by 2 experts from DWI (or NCCT if DWI was unavailable). Follow-up images along with manual infarct segmentations were then co-registered onto the CTP average maps using affine registration in the NiftyReg tool,[12] followed by manual corrections of the registered infarct segmentation using ITK-SNAP if registration was suboptimal.

For the independent test cohort of 137 patients from the HERMES collaboration, the infarct region on follow-up was delineated by the HERMES Imaging Core laboratory, using a previously validated software followed by manual corrections when appropriate.[13] The ischemic core volume at baseline was also estimated using relative CBF threshold (relative cerebral blood flow [rCBF] <0.3) with RAPID (iSchemaView, Menlo Park, CA) by the HERMES Imaging Core laboratory,[5,13] and time-dependent T_{max} thresholds.[10]

ML Model

We used a random forest classifier to predict infarct probability for each voxel. The RF classifier maps multiple CTP parameters of each voxel as well as time variables to a statistical infarction probability model at a voxel level. Specifically, CTP average maps, T_{max}, CBF, and cerebral blood volume were smoothed using median filtering and then normalized using *Z*-score method. In addition to CTP parameters at a voxel level, patient-specific time factors such as stroke symptom onset-to-imaging and imaging-to-reperfusion time were also used. The 4 CTP parameters for each voxel and the 2 time factors for that individual patient were used as features to train a voxel-wise ML model using random forest while using manual segmentations of follow-up infarct as responses (1: infarct, 0: normal tissue). The ML model and the associated parameters were trained and optimized using 5-fold cross validation with 68 patient images from the PRoveIT study. The number of trees for the random forest model was 80, the depth of trees was 10, bootstrapping was used, and the class weights for infarct and normal tissue were automatically assigned based on the actual distributions of samples. When the trained ML model is applied on to a new subject image, it is able to generate infarct probabilities for each voxel, thereby classifying each voxel as infarct or not (0.5 as cutoff). The derived ML model was then independently tested on 137 patients from the HERMES collaboration to assess performance volumetrically and spatially.

Stroke. 2021;52:223–231. DOI: 10.1161/STROKEAHA.120.030092

Statistical Analysis

Agreement between the baseline infarct generated by the proposed CTP-based RF model (ML infarct) and follow-up infarct manually segmented from DWI/NCCT was assessed by Dice similarity coefficient and volumetric difference defined as the actual follow-up infarct volume minus the infarct volume estimated by the ML method. Bland-Altman plots were reported. The association between predicted infarct volume from the ML model and follow-up infarct volume was analyzed using Pearson correlation coefficient. In addition, sensitivity analyses on volumetric difference were performed by stratifying patients into 3 groups based on CTP imaging-to-reperfusion time: (1) ≤90 minute reperfusion, (2) 90–180 minute reperfusion, and (3) no acute reperfusion within 180 minutes after baseline CTP acquisition, and 2 groups based on symptom onset to CTP imaging time: (1) ≤180 minutes and (2) >180 minutes.

In particular, to compare the derived ML model over a fixed CTP thresholding (rCBF<0.3) and time-dependent CTP thresholding (T_{max}) estimation, the ML infarct volume was compared with the infarct volume measured by rCBF<0.3 threshold using RAPID (RAPID volume) and time-dependent T_{max} thresholds[10] (time-dependent T_{max} volume) in 137 patients from the HERMES collaboration, using follow-up infarct volume as the reference. The Shapiro-Wilk test was used to test the normality of data. Differences among nonparametric data were assessed by ANOVA, followed by the Tukey-Kramer multiple comparison method. Differences between Pearson correlation coefficients were calculated using Fisher r-to-z transformation. The 3 techniques were also compared by dichotomizing follow-up infarct volume using thresholds of 70 and 100 mL.

A 2-sided alpha <0.05 was considered as statistically significant. All statistical analyses were performed using MedCalc 17.8 (MedCalc Software, Mariakerke, Belgium) and Matlab (The MathWorks, Inc).

RESULTS

Patient Characteristics

Patient characteristics of the 68 patients for deriving the ML model and 137 patients for testing are detailed in Table 1. Of 68 patients in the derivation cohort, 12 patients had follow-up NCCT and 56 had follow-up DWI scans. Of 137 patients for testing, 99 patients had follow-up NCCT and 38 had follow-up DWI scans. Median time from stroke symptom onset-to-imaging was 141 minutes (interquartile range [IQR], 90–271 minutes). Median time from CTP imaging-to-reperfusion was 143 minutes (IQR, 108–221 minutes).

Volumetric and Spatial Agreement of the ML Model Predicted Infarct

The median baseline predicted final infarct volume from the ML model was 30.9 mL (IQR, 16.4–54.3 mL), compared with an actual median follow-up infarct volume of 29.6 mL (IQR, 11.1–70.9 mL). Infarct volume estimated using the ML method correlated positively with the follow-up infarct volume (Pearson correlation coefficient: 0.80 [95% CI, 0.74–0.86]; $P<0.001$) in Figure 1A. Bland-Altman plots show that the mean volumetric difference between follow-up infarct volume and ML infarct volume was −3.1 mL (Limits of agreement, −59.9 to 53.7 mL; Figure 1B). The median volumetric difference between infarct volume estimated using the ML method and follow-up infarct was −3.2 mL (IQR, −16.7 to 6.1 mL). The median Dice similarity coefficient between infarct volume estimated using the ML method and follow-up infarct was 38.8% (IQR, 19.2%–54.1%). Figure 2 shows the prediction results using the ML method for 3 patients with imaging-to-reperfusion time of <90 minutes, 90 to 180 minutes, and >180 minutes, respectively. Of 137 patients, the ML model underestimated the follow-up infarct volume in 88 patients, and overestimated the follow-up infarct volume in 49 patients.

Table 1. Patient Characteristics for Training and Test Datasets

Characteristics	Training data from PRoveIT (N=68)	Testing data from HERMES (N=137)
Median age, y (IQR)	69 (59–79)	65 (56–77)
Sex, male; No. (%)	31 (46)	61 (45)
Median baseline NIHSS (IQR)	16 (8–20)	17 (14–20)
Median onset-to-imaging time (IQR), min	135 (104–274)	141 (90–217)
Median imaging-to-reperfusion time (IQR), min	160 (81–286)	143 (108–221)
Median onset-to-reperfusion time (IQR), min	317 (218–543)	306 (233–399)
Median follow-up infarct volume (IQR), mL	24.1 (7.6–60.1)	29.6 (11.1–70.9)
Median RF infarct volume (IQR), mL	NA	30.9 (16.4–54.3)
Median rCBF<0.3 infarct volume (IQR), mL	NA	13.4 (3.4–33.7)
Median time dependent T_{max} infarct volume (IQR), mL	NA	39.9 (19.9–71.5)
Site of occlusion at baseline, No. (%)		
ICA	23 (34)	44 (32)
MCA:M1	35 (51)	77 (56)
Other	10 (15)	16 (12)

HERMES indicates Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials; ICA, internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PRoveIT, Measuring Collaterals With Multi-Phase CT Angiography in Patients With Ischemic Stroke; rCBF, relative cerebral blood flow; and RF, random forest.

Comparisons to rCBF<0.3 (RAPID) and Time-Dependent T_{max} Thresholds

The baseline median infarct volume predicted by rCBF<0.3 of RAPID was 13.4 mL (IQR, 3.4–37.3mL), and by the time-dependent T_{max} thresholds was 39.9 mL (IQR, 19.9–71.5 mL), compared with an actual median 29.6 mL (IQR, 11.1–70.9 mL) of follow-up infarct volume. The association between the ML predicted final infarct volume (r=0.80 [95% CI, 0.74–0.86) and follow-up infarct volume was stronger when compared with that between rCBF<0.3

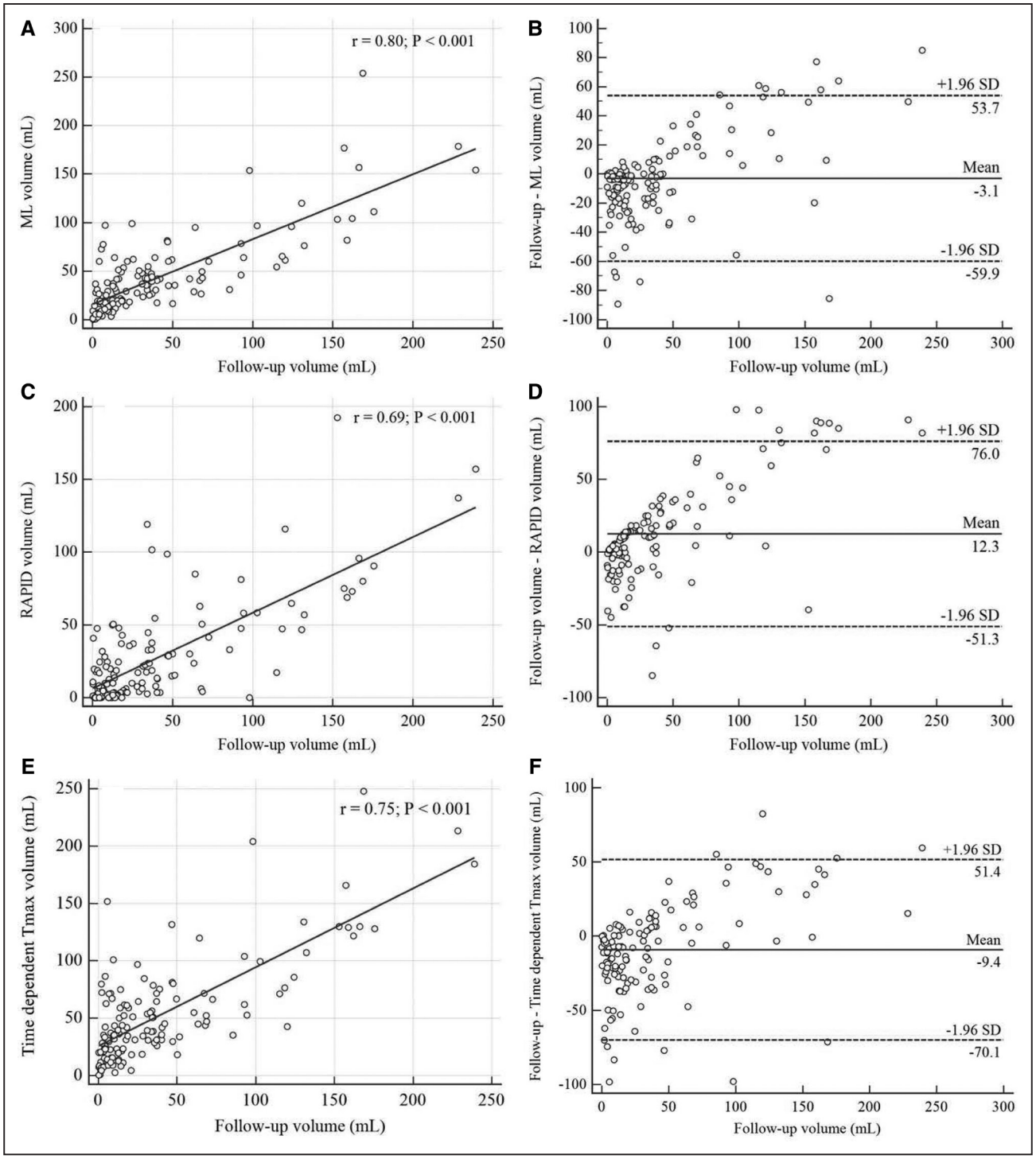

Figure 1. Volumetric agreement of the infarct volume estimated by the 3 methods compared to the follow-up infarct volume. Association (**A**) and Bland-Altman plot (**B**) between the computed tomography perfusion–based machine learning (ML) model estimated infarct volume (ML volume) and follow-up infarct volume (follow-up volume). Association (**C**) and Bland-Altman plot (**D**) between the infarct volume predicted by relative cerebral blood flow <0.3 threshold (RAPID volume) and follow-up infarct volume. Association (**E**) and Bland-Altman plot (**F**) between the infarct volume predicted by time-dependent Tmax thresholds (discrete time volume) and follow-up infarct volume.

infarct volume and follow-up infarct (r=0.69 [95% CI, 0.60–0.79]; P=0.040) or time-dependent T_{max} thresholded volume and follow-up infarct volume (r=0.75 [95% CI, 0.69–0.80]; P=0.152; Figure 2A, 2C, 2E). Bland-Altman plots show that the mean volumetric difference was −3.1 mL (limits of agreement, −59.9 to 53.7 mL, Figure 1B) between the ML infarct volume and follow-up infarct volume; this was smaller than between RAPID infarct volume and follow-up infarct volume (12.3 mL; limits of agreement, −51.3 to 76.0 mL, Figure 1D) and time-dependent T_{max}

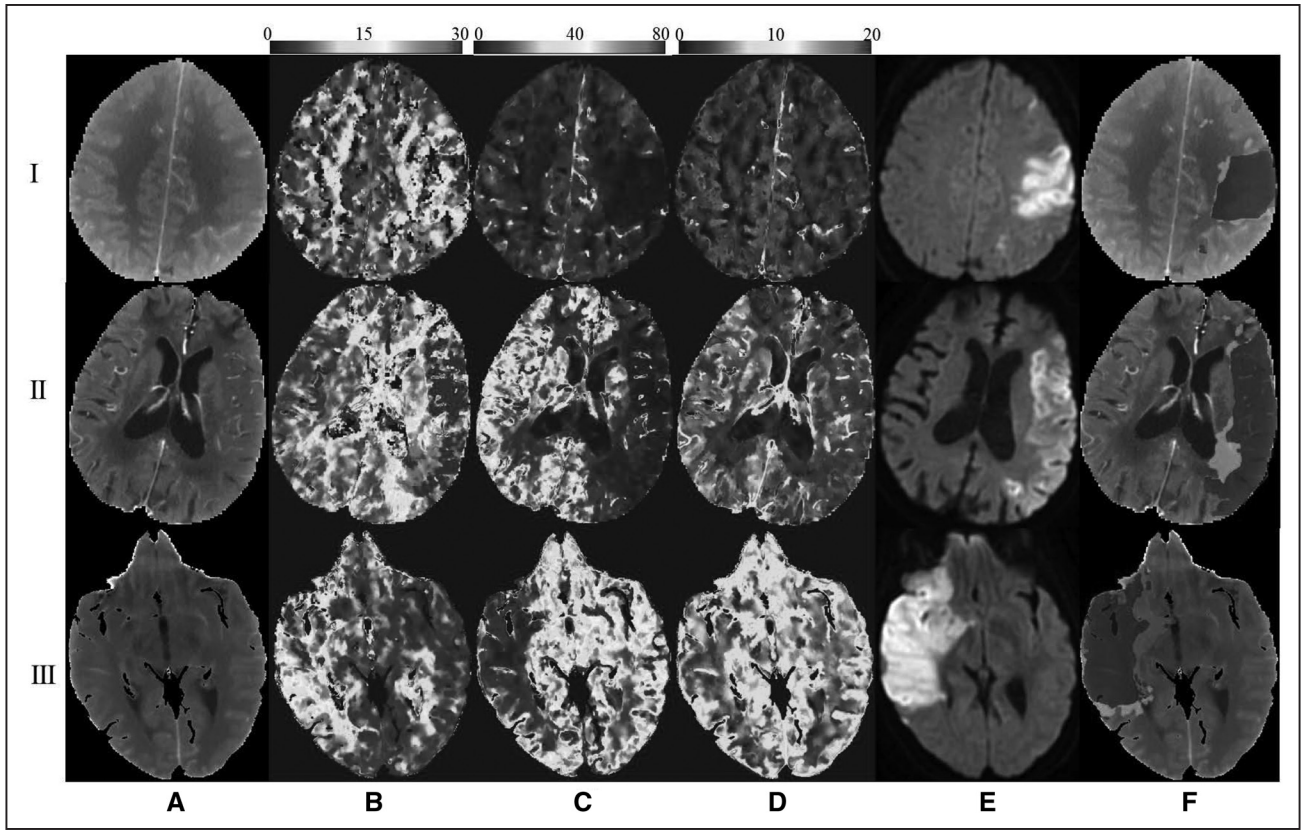

Figure 2. Infarct prediction for 3 patients (rows I, II, and III) using the derived machine learning model.
These patients are with the imaging-to-reperfusion time: 0 to 90 min (I), 90 to 180 min (II), and >180 min (III), respectively. Column (**A**)–(**E**) denote average map, Tmax, cerebral blood flow, and cerebral blood volume (CBV), and follow-up diffusion-weighted imaging (DWI), respectively. Column (**F**) shows the prediction results, in which dark color voxels are the algorithm predicted follow-up infarction that matches with actual follow-up infarction while light color voxels are under- and overestimation of infarction by the algorithm when compared with actual follow-up infarction on DWI.

volume and follow-up infarct volume (−9.4 mL; limits of agreement, −70.1 to 51.4 mL, Figure 1F).

Volumetric difference between the 3 methods and follow-up infarct volume for all 137 patients are shown in Table 2. For all 137 patients, volumetric difference (median, −3.2 mL; IQR, −16.7 to 6.1 mL; ANOVA $P<0.001$) with the ML method was smaller than with rCBF<0.3 threshold (median, 8.0 mL; IQR, −2.3 to 20.2 mL), and time-dependent T_{max} threshold (median, −10.6 mL; IQR, −53.9 to 20.0 mL). When patients were stratified by stroke onset-to-imaging and imaging-to-reperfusion time, the variance in volume difference between the predicted follow-up infarct volume and the actual follow-up infarct volume was on average least with the ML model (Table 2).

When all 137 patients were dichotomized using a follow-up infarct volume of 70 mL, the prediction accuracy of the 3 methods is demonstrated in Table 3. The AUC of the ML method was 0.81 (95% CI, 0.69–0.90), when compared with the rCBF<0.3 threshold (0.71 [95% CI, 0.61–0.82]) and the time-dependent T_{max} threshold method (0.75 [95% CI, 0.67–0.85]). When the 137 patients were dichotomized using a follow-up infarct volume of 70 mL, the ML model miss-classified 6 out of 22 patients with follow-up infarct >70 mL, and 8 out of 115 patients with follow-up infarct volume ≤70 mL. The ML algorithm underestimated infarct volume in patients with longer onset-to-imaging and imaging-to-reperfusion time and overestimated infarct volume in patients with shorter onset-to-imaging and imaging to reperfusion time.

When the onset-to-imaging and imaging-to-reperfusion time were not used to train the ML model, the volumetric agreement of the ML model predicted infarct was poorer than that of using the 2 time to train the ML model (see Tables I–II and Figure I in the Data Supplement), which showed the 2 time was helpful to improve the accuracy of predicting follow-up infarction.

DISCUSSION

Ischemic tissue state estimation at baseline in patients with AIS is based on univariate CT perfusion parameter thresholding, such as rCBF<0.3 using RAPID. Recent studies, however, show that discrete CTP thresholds that estimate follow-up infarction, such as T_{max} or CBF, likely depend on time from imaging to quality reperfusion.[6,7,10] In this analysis, we show that ML techniques using multiple CTP parameters along with continuous time variables such as stroke symptom onset-to-imaging and imaging-to-reperfusion time predict follow-up infarct volume significantly better than with discrete CTP thresholds. This

Table 2. Volumetric Difference (Actual–Estimated Follow-Up Infarction) for the 3 CTP Prediction Methods When Applied to All 137 Patients and Within Subgroups Stratified by Onset-to-Imaging and Imaging-to-Reperfusion Time

Metric	Subgroup		Machine learning model	Time-dependent T_{max} thresholds	rCBF<0.3 using RAPID	*P* value (ANOVA)	*P* value (ML vs time-dependent T_{max})	*P* value (ML vs RAPID)	*P* value (time-dependent T_{max} vs RAPID)
Volumetric difference (actual–estimated follow-up infarction; median and IQR)	All patients (n=137)		−3.2 (−16.7 to 6.1)	−10.6 (−53.9 to 20.0)	8.0 (−2.3 to 20.2)	<0.001	0.475	<0.001	<0.001
	Onset-to-imaging time, min	≤180 (n=91)	−4.5 (−18.9 to 0.8)	−7.0 (−18.5 to 8.1)	2.1 (−9.1 to 13.9)	0.001	0.961	0.003	0.007
		>180 (n=46)	−0.1 (−8.5 to 15.9)	3.3 (−8.2 to 26.0)	18.6 (8 to 44.3)	<0.001	0.807	<0.001	0.006
	Imaging-to-reperfusion time, min	<90 (n=20)	−1.9 (−14.4 to 4.7)	−8.3 (−33.3 to 10.5)	5.5 (−4.8 to 10.8)	0.071	0.821	0.233	0.066
		90 to 180 (n=63)	−3.3 (−15.6 to 0.2)	−23.3 (−55.2 to 1.1)	1.6 (−15.6 to 16.7)	<0.001	0.021	0.298	<0.001
		>180 (n=53)	−3.7 (−19.2 to 13.0)	0.20 (−43 to 47.7)	14 (3.8 to 48.7)	<0.001	0.456	<0.001	0.024

CTP indicates computed tomography perfusion; IQR, interquartile range; ML, machine learning; and rCBF, relative cerebral blood flow.

threshold-free CTP prediction technique can be useful for physicians to estimate probability of infarction conditional on when they estimate reperfusion is likely to be achieved.

The CTP-based ML model described here was derived using data from 68 patients, but at a voxel level (around 68×512×512×16=2.9G voxels), and was independently tested on a separate dataset of 137 patients from the HERMES collaboration. The derived ML model generated smaller volumetric difference versus follow-up infarct volumes for all 137 patients and in most subgroups stratified by onset-to-imaging time and imaging-to-reperfusion time, when compared with current methods like the discrete rCBF <0.3 threshold or the discrete time-dependent T_{max} thresholds (Table 2). As a corollary to greater precision of final tissue fate volume estimation, the ML model generated better accuracy in predicting patients with a dichotomized follow-up infarct volume at the commonly used threshold of >70 versus <70 mL than rCBF<0.3 and time-dependent T_{max} thresholds. A caveat to these results is the concept that the discrete rCBF <0.3 threshold estimates infarction at the time of imaging; it therefore is likely to underestimate follow-up infarction, especially in patients who do not achieve early reperfusion.[2] Indeed, as shown in Table 2, these results support that premise; rCBF<0.3 threshold underestimates infarct volume by a median 18.6 mL when symptom onset-to-imaging time is >180 minutes and by a median 14 mL when imaging-to-reperfusion time is >180 minutes. In comparison, the discrete time-dependent T_{max} thresholds estimate follow-up infarction. These results show that, on average, this latter method tends to overestimate infarct volume in the very early

Table 3. Comparison of the 3 CTP Prediction Methods When Predicting Actual Follow-Up Infarct Volume (70 or 100 mL)

Volume threshold	Metric	Machine learning model	Time-dependent T_{max} thresholds	rCBF<0.3 using RAPID
>70 vs ≤70 mL	Accuracy	89.8 (123/137)	83.9 (115/137)	88.3 (121/137)
		(83.1–94.2)	(76.5–89.6)	(81.4–93.1)
	Sensitivity	72.7 (16/22)	63.6 (14/22)	45.5 (10/22)
		(63.6–79.8)	(54.4–70.2)	(37.0-54.2)
	Specificity	93.0 (107/115)	87.8 (105/115)	96.5 (111/115)
		(88.1–97.3)	(86.2–95.4)	(91.3–99.0)
	AUC	0.81 (0.69–0.90)	0.75 (0.67–0.85)	0.71 (0.61–0.82)
>100 vs ≤100 mL	Accuracy	94.2 (129/137)	89.1 (122/137)	89.8 (123/137)
		(88.4–97.5)	(82.3–93.7)	(83.1–94.2)
	Sensitivity	56.3 (9/16)	68.8 (11/16)	25.0 (4/16)
		(47.5–64.6)	(51.3–72.4)	(18.2–33.2)
	Specificity	99.2 (120/121)	91.7 (111/121)	98.3 (119/121)
		(95.5–100)	(85.3–96.0)	(94.2–99.8)
	AUC	0.78 (0.64–0.90)	0.76 (0.61–0.88)	0.61 (0.53–0.74)

Results are shown as % metric with 95% CI for accuracy, sensitivity, and specificity. Also reported is AUC of receiver operating characteristic curve with 95% CI. Positive cases were defined as subjects with actual follow-up infarct volume >70 or >100 mL. AUC indicates area under curve; CTP, computed tomography perfusion; and rCBF, relative cerebral blood flow.

presenters, that is, with stroke onset-to-imaging time <180 minutes, by around 7 mL on average. This is likely because the statistical models used here do not account for short onset-to-imaging or reperfusion times in as granular a manner as the ML models do.[14,15] By using all available data from the different CTP parameters and time as a continuous variable, this threshold-free ML model demonstrates an ability to estimate follow-up infarction conditional on reperfusion status more robustly than current methods. Figure 3 is an example showing the use of the proposed ML model to estimate follow-up infarct volume at different time intervals to reperfusion.

Endovascular treatment become the standard of care in patients with disabling AIS because of large vessel occlusions. However, patients with large ischemic core are less likely to benefit from this therapy. It is therefore important that physicians are able to estimate the extent of brain that will likely infarct even if early reperfusion is achieved. In addition, physicians in primary stroke centers without endovascular treatment capability will benefit from knowing how much brain tissue is likely to infarct during the time a patient is transported to an endovascular treatment capable tertiary hospital. Our analysis demonstrates that CTP based threshold-free ML models can provide physicians with reasonably accurate probability maps overlaid on images of the brain that may help them estimate infarct growth over time, thereby helping make appropriate triage, transport and treatment decisions about endovascular treatment.

This study has limitations. First, Dice similarity coefficient between the ML infarct and follow-up infarct seems low (38.8%). This might be explained by the limitations inherent in current image post-processing such as co-registration of images across different imaging modalities. These results are however superior to spatial correlation metrics reported from the HERMES group that used a rCBF<0.3 threshold and compared estimated infarct to follow-up infarction and validated CTP software (median Dice similarity coefficient, 24%; IQR, 15%–37%).[2] Second, a majority of follow-up scans for validation in this study were NCCT. Follow-up infarct segmentation were performed using a semiautomated method with manual input of corrections when necessary. More images with precise segmentations of follow-up infarct on magnetic resonance imaging (DWI/fluid attenuated inversion recovery) may increase the validity of the derived CTP-based ML model. Third, only a small number of patients with acute reperfusion were used to derive the ML model.

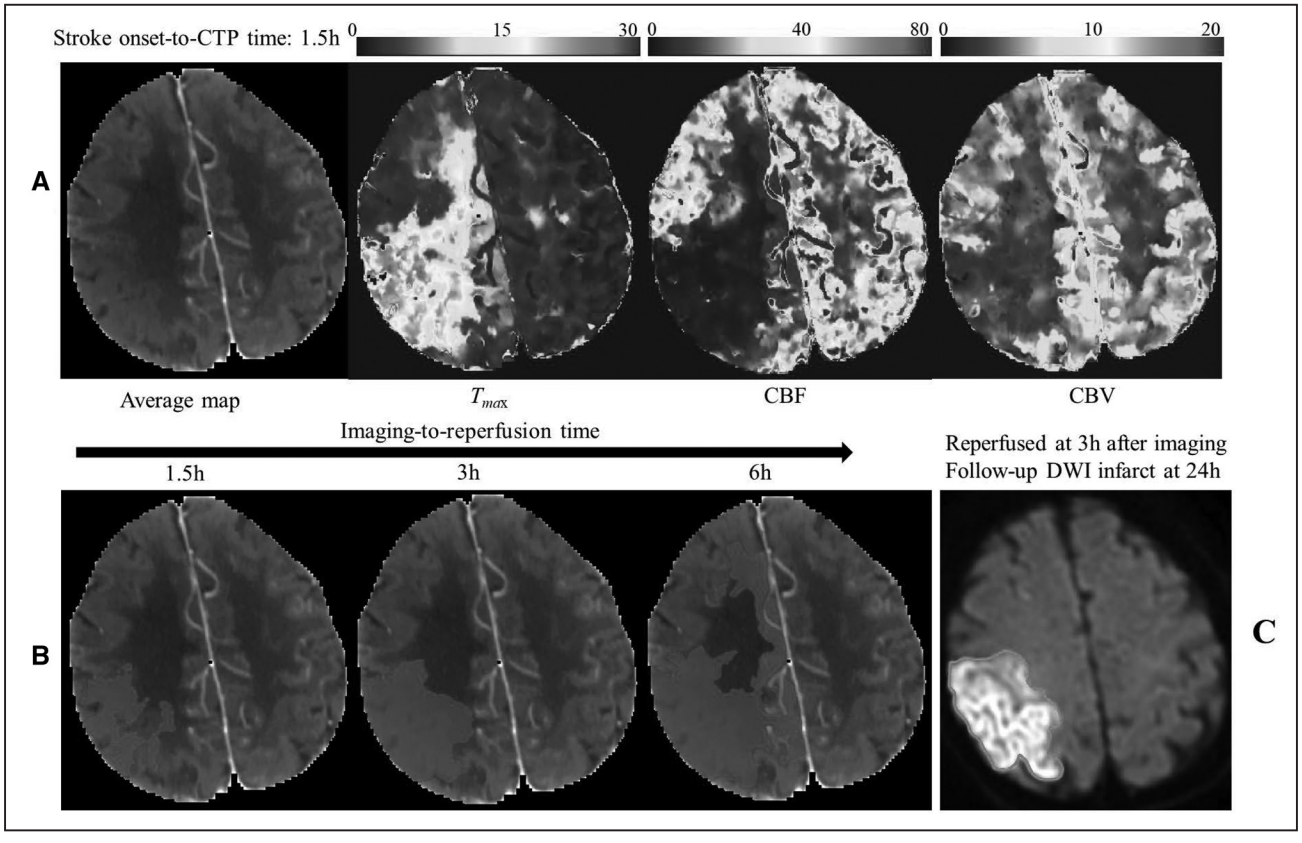

Figure 3. Prediction results by different imaging-to-reperfusion times using the computed tomography perfusion (CTP)-based machine learning model.

A, Baseline CTP imaging; (**B**) prediction results by changing the parameter of imaging-to-reperfusion time intervals to 1.5, 3, and 6 h in the machine learning model; (**C**) 24 h follow-up diffusion-weighted imaging (DWI) with infarct contoured in the patient who reperfused at 3 h after CTP imaging. CBF indicates cerebral blood flow.

More images for training may allow for more accurate and robust infarct prediction. Fourth, the ML model may improve further with use of other relevant clinical and imaging variables. Finally, CTP imaging is more established for selecting patients in the late time window (6–24 hours, DAWN [DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention]/DEFUSE [Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke]). However, most of the patients used in this study underwent imaging and reperfusion within 6 hours (or earlier) from stroke symptom onset. Extensive validation of the derived ML model in patients presenting in the late time window is needed.

In conclusion, a CTP based threshold-free ML model is capable of predicting follow-up infarction at baseline in patients with AIS better than current methods that use fixed thresholding of a single CTP parameter or discrete time-dependent CTP thresholds.

ARTICLE INFORMATION

Received May 29, 2020; final revision received August 13, 2020; accepted October 8, 2020.

Affiliations

Department of Clinical Neurosciences (H.K., W.Q., M.D.H., A.M.D., M.G., B.K.M.), Department of Radiology (M.D.H., A.M.D., M.G., B.K.M.), and Hotchkiss Brain Institute (M.D.H., A.M.D., M.G., B.K.M.), University of Calgary. Department of Biomedical Engineering and Physics (A.M.B.) and Department of Radiology and Nuclear Medicine (C.B.L.M.M.), Amsterdam University Medical Centre. Altair Biostatistics, Mooresville, NC (S.B.). Institute of Neuroscience and Psychology, University of Glasgow, Queen Elizabeth University Hospital (K.M.). Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centre (C.B.L.M.M.). Department of Neurology, Erasmus University Medical Center (D.W.J.D.). Institute of Neuroscience, Newcastle University (P.W.). Centre Hospitalier Régional et Universitaire de Nancy, Université de Lorraine (J.E.). Department of Radiology, Royal Melbourne Hospital, University of Melbourne (P.J.M.). Department of Neuroscience, Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona (A.D.). IADI, Inserm, Université de Lorraine, CHRU-Nancy, France (S.B.). Department of Diagnostic and Interventional Neuroradiology, Nancy, France (S.B.). Department of Medicine and Neurology, Royal Melbourne Hospital, University of Melbourne (B.C.). David Geffen School of Medicine, University of Los Angeles (J.L.S.). Cooper Neurological Institute (T.G.J.). Department of Neurology, Hospital Vall d'Hebron, Ps. Vall d'Hebron, Barcelona, Spain (M.R.). Department of Clinical Neurosciences, University of Western Ontario, London, Canada (A.V.K.). Department of Radiology, University of Manitoba, Winnipeg, Canada (J.J.S.). Department of Experimental and Clinical Biomedical Sciences "Mario Serio", University of Florence, Italy (E.F.).

Sources of Funding

Dr Menon holds the Heart and Stroke/University of Calgary Professorship in Stroke Imaging and Alberta Innovate Health Solution funding.

Disclosures

Dr Menon reports other from Circle NVI and the Canadian Institute Health Research during the conduct of the study; in addition, Dr Menon has a patent to Systems of triage in acute stroke issued. Dr Boers reports stock in Nico-lab B.V. Dr Brown reports personal fees from University of Calgary during the conduct of the study; personal fees from Medtronic outside the submitted work. Dr Demchuk reports other from Circle NVI outside the submitted work; in addition, Dr Demchuk has a patent to Circle NVI issued. Dr Dippel reports grants from Dutch Heart Foundation, grants from Brain Foundation Netherlands, grants from The Netherlands Organisation for Health Research and Development, grants from Health Holland Top Sector Life Sciences & Health, grants from Stryker European Operations BV, grants from Penumbra, Inc, grants from Medtronic, grants from Thrombolytic Science, LLC, and grants from Cerenovus outside the submitted work. Dr Goyal reports personal fees from Medtronic, personal fees from Stryker, personal fees from Mentice, and personal fees from Microvention outside the submitted work; in addition, Dr Goyal has a patent to Systems of acute stroke diagnosis issued and licensed. Dr Hill reports grants from Medtronic LLC during the conduct of the study; grants from NoNO, Inc outside the submitted work; in addition, Dr Hill has a patent to US Patent office Number: 62/086,077 issued and licensed; and Director, Circle Neurovascular; Director, Canadian Stroke Consortium; Director, Canadian Neuroscience Federation. Dr Jovin reports other from Anaconda, other from Route92, other from Vizai, other from FreeOx, other from Stryker Neurovascular, other from Blockade Medical, other from Corindus, and personal fees and other from Cerenovus outside the submitted work. Dr Majoie reports grants from CVON/Dutch Heart Foundation, grants from European Commission, grants from TWIN Foundation, and grants from Stryker outside the submitted work; and Shareholder of Nicolab, a company that focuses on the use of artificial intelligence for medical image analysis. Dr Muir reports personal fees and nonfinancial support from Boehringer Ingelheim, personal fees from Bayer, personal fees from Daiichi Sankyo, and personal fees from ReNeuron outside the submitted work. Dr Saver reports personal fees from Medtronic, personal fees from Stryker, personal fees from Cerenovus, and personal fees from Rapid Medical outside the submitted work; and Dr Saver is an employee of the University of California. The University of California has patent rights in retrieval devices for stroke. Dr White reports grants from Microvention, grants from Stryker, grants from Medtronic, grants from Penumbra, and personal fees from Microvention outside the submitted work. Dr Epstein reports other from the French Ministry for Health during the conduct of the study. The other authors report no conflicts.

Supplemental Materials

Results
Tables I–II
Figure I

REFERENCES

1. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Hanel RA, et al; DAWN Trial Investigators. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378:11–21. doi: 10.1056/NEJMoa1706442
2. Hoving JW, Marquering HA, Majoie CB, Yassi N, Sharma G, Liebeskind DS, van der Lugt A, Roos YB, van Zwam W, van Oostenbrugge RJ, et al. Volumetric and spatial accuracy of computed tomography perfusion estimated ischemic core volume in patients with acute ischemic stroke. *Stroke*. 2018;49:2368–2375. doi: 10.1161/STROKEAHA.118.020846
3. Campbell BC, Christensen S, Levi CR, Desmond PM, Donnan GA, Davis SM, Parsons MW. Cerebral blood flow is the optimal CT perfusion parameter for assessing infarct core. *Stroke*. 2011;42:3435–3440. doi: 10.1161/STROKEAHA.111.618355
4. Bivard A, Levi C, Spratt N, Parsons M. Perfusion CT in acute stroke: a comprehensive analysis of infarct and penumbra. *Radiology*. 2013;267:543–550. doi: 10.1148/radiol.12120971
5. Mokin M, Levy EI, Saver JL, Siddiqui AH, Goyal M, Bonafé A, Cognard C, Jahan R, Albers GW. Predictive value of rapid assessed perfusion thresholds on final infarct volume in swift prime (solitaire with the intention for thrombectomy as primary endovascular treatment). *Stroke*. 2017;48:932–938. doi: 10.1161/STROKEAHA.116.015472
6. Bivard A, Kleinig T, Miteff F, Butcher K, Lin L, Levi C, Parsons M. Ischemic core thresholds change with time to reperfusion: a case control study. *Annals of neurology*. 2017;82:995–1003
7. d'Esterre CD, Boesen ME, Ahn SH, Pordeli P, Najm M, Minhas P, Davari P, Fainardi E, Rubiera M, Khaw AV, et al. Time-dependent computed tomographic perfusion thresholds for patients with acute ischemic stroke. *Stroke*. 2015;46:3390–3397. doi: 10.1161/STROKEAHA.115.009250
8. Menon BK, d'Esterre CD, Qazi EM, Almekhlafi M, Hahn L, Demchuk AM, Goyal M. Multiphase CT angiography: a new tool for the imaging triage of patients with acute ischemic stroke. *Radiology*. 2015;275:510–520. doi: 10.1148/radiol.15142256
9. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CB, van der Lugt A, de Miquel MA, et al; HERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731. doi: 10.1016/S0140-6736(16)00163-X

10. Qiu W, Kuang H, Lee TY, Boers AM, Brown S, Muir K, Majoie CBLM, Dippel DWJ, White P, Guillemin F, et al. Confirmatory study of time-dependent computed tomographic perfusion thresholds for use in acute ischemic stroke. *Stroke*. 2019;50:3269–3273. doi: 10.1161/STROKEAHA.119.026281
11. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20. doi: 10.1056/NEJMoa1411587
12. Modat M, Ridgway GR, Taylor ZA, Lehmann M, Barnes J, Hawkes DJ, Fox NC, Ourselin S. Fast free-form deformation using graphics processing units. *Comput Methods Programs Biomed*. 2010;98:278–284. doi: 10.1016/j.cmpb.2009.09.002
13. Boers AMM, Jansen IGH, Beenen LFM, Devlin TG, San Roman L, Heo JH, Ribó M, Brown S, Almekhlafi MA, Liebeskind DS, et al. Association of follow-up infarct volume with functional outcome in acute ischemic stroke: a pooled analysis of seven randomized trials. *J Neurointerv Surg*. 2018;10:1137–1142. doi: 10.1136/neurintsurg-2017-013724
14. Qiu W, Kuang H, Menon BK. Response by qiu et al to letter regarding article," confirmatory study of time-dependent computed tomographic perfusion thresholds for use in acute ischemic stroke". *Stroke*. 2019;51:e8. doi: 10.1161/STROKEAHA.119.027910
15. Najm M, Al-Ajlan FS, Boesen ME, Hur L, Kim CK, Fainardi E, Hill MD, Demchuk AM, Goyal M, Lee TY, et al. Defining CT perfusion thresholds for infarction in the golden hour and with ultra-early reperfusion. *Can J Neurol Sci*. 2018;45:339–342. doi: 10.1017/cjn.2017.287