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CTP based Model predicts Outcome in rTPA treated Wake-up Stroke Patients

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Running title: CTP model predicts WUS outcome

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Abstract:

Objective Advanced Neuroimaging has been proving to be pivotal in acute ischemic stroke management. CT Perfusion (CTP) core and penumbra parameters have not yet been investigated to predict the outcome in Wake-up Stroke (WUS) patients in everyday clinical scenario. The aim of our study is to investigate the predictive power of CTP-parameters on functional and morphological outcomes in rTPA treated WUS patients. **Approach** We analyzed clinical data and processed CTP images of 80 consecutive WUS rTPA treated patients. The predictive power of whole-brain CTP features and of the clinical stroke related parameters to predict NIHSS at 7th day and Ischemic Lesion Volume outcome was investigated by means of multivariate regression analysis as well as LASSO modeling. **Main results** Multivariate analysis showed that CTP core volume (β: 0.403, p= 0.000), NIHSS at admission (β: 0.323, p= 0.005) and ASPECTS (β: -0.224, p= 0.012) predict NIHSS at 7-days, while total hypoperfused volume (β: 0.542, p= 0.000) and core volume on CTP (β: 0.441, p= 0.000) predict infarct lesion volume at follow-up CT. The LASSO modeling approach confirmed the significant predictive power of CTP core volume, CTP total hypoperfused, NIHSS at baseline and ASPECTS producing a sparse model with adequate reliability (RMSE on previously unseen testing dataset was 3.68). **Significance** Our findings highlight the importance of CT multimodal imaging features in the decision-making and predictivity in the hyperacute phase of WUS. The predictive model supports the hypothesis that irreversible necrotic core rather the extent of penumbra is the main prognostic determinant in rTPA treated WUS patients.

Keywords: Wake-up Stroke; Thrombolysis; Ischemic Volume Lesion; CT Perfusion; Image processing;

Abstract words count 250

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1. INTRODUCTION

Wake-up Stroke (WUS) represents around a quarter of acute ischemic stroke events (Denny MC *et al* 2014, Mackey *et al* 2011, Rubin and Barrett 2015, Thomalla *et al* 2014). If stroke onset is known, current guidelines limit the time to initiate intravenous thrombolysis (rTPA) therapy to maximum 4.5 hours from the stroke onset (Powers *et al* 2018). In everyday clinical practice, a considerable portion of WUS patients is generally excluded from thrombolytic therapy due to the unknown time of stroke onset (Barreto *et al* 2016, Kang *et al* 2012).

Neuroimaging is a cornerstone in ischemic stroke diagnosis and it is crucial for patients' eligibility for treatment (Vilela and Rowley 2017, Lewandowski and Libman 1999, Furlanis *et al* 2018, Manganotti *et al* 2019). MRI- or CT Perfusion- (CTP) based neuroimaging can identify patients who can most benefit from the recanalization treatment by identifying irreversible infarct core and the ischemic salvageable penumbra area in a quick and accurate manner (Gonzalez 2006). In emergency settings, decision-making is always more based on the *tissue clock* approach instead of on the *time clock* approach. Neuroimaging-based patient selection methods have, indeed, shown their ability to identify additional populations of stroke patients that could benefit from late-window reperfusion therapy, included in wake-up stroke patients (Etherton *et al* 2018, Ma *et al* 2019, Thomalla *et al* 2018, Caruso *et al* 2018, Furlanis *et al* 2019).

The WAKE-UP trial demonstrated the benefit of rTPA treatment in WUS patients by identifying an MRI DWI/FLAIR pattern suggestive of stroke with an onset of less than 4.5 hours (Thomalla *et al* 2018). The recent EXTEND trial based on CTP or PWI/DWI - MRI imaging, showed that rTPA administered in patients admitted between 4.5 and 9.0 hours after stroke onset or in WUS parients resulted in better functional outcome than the use of placebo (Ma *et al* 2019).

The aforementioned studies included well-selected WUS patients in terms of time window and advanced neuroimaging parameters. CTP assessed core, penumbra and their ratio has been proving to be pivotal in acute ischemic stroke decision-making both in known onset stroke (Agarwal *et al* 2011, Bivard *et al* 2018, Campbell *et al* 2019, Ryu *et al* 2017, Kawano *et al* 2017) and in WUS (Ma *et al* 2019, Caruso *et al* 2018). However, these parameters have not yet been investigated to predict the outcome in rTPA-treated WUS patients in everyday clinical scenario. The aim of our study is to investigate the predictive power of core and penumbra parameters assessed by CTP processing, and final neurological deficit and infarct volume in rTPA treated WUS patients.

2. METHODS

We processed CT images and analyzed clinical data of patients with acute ischemic stroke developed at morning awakening who underwent reperfusion treatment, admitted within 4.5 hours from awakening to the Stroke Unit of the University Medical Hospital of Trieste (Italy) between March 2016 and June 2019. No age limit was applied and both genders were included. Hemorrhagic stroke patients, patients with thrombolysis treatment contraindications and patients who were eligible but refused the treatment were excluded. Stroke mimics was excluded by a complete diagnostic work-up including clinical and MRI assessment to confirm the absence of ischemic lesion.

The included patients underwent rTPA treatment after fulfillment of eligibility criteria defined by the new standardized protocol for diagnosis and treatment of acute stroke of the Trieste University Hospital introduced in March 2016. Thanks to the advanced multiparametric CT assessment, the new rTPA protocol includes WUS patients arriving within 4 hours from awakening with ASPECT score >6 and ischemic penumbra >50% of the whole ischemic tissue on CTP and current inclusion clinical criteria for rTPA administration. Patients eligible for thrombolysis were treated with intravenous rtPA (0.9 mg/kg of body weight, maximum of 90 mg, infused over 60 minutes with 10% of the total dose administered as an initial intravenous bolus over 1 minute). Mechanical endovascular treatment (EVT) was performed in patients with M1, M2, A1, ICA and basilar artery upon clinical evaluation of the interventional neuroradiologist and according to standard clinical practice. Non-enhanced CT (NECT), Angio-CT, CT Perfusion at admission and a follow-up NECT were performed in all included patients. Moreover a common neurologic stroke work-up including assessment of stroke risk factors, electrocardiography, carotid ultrasound, echocardiography and Holter-electrocardiography or telemetric ECG-monitoring. The Trial of Org 1072 in Acute Stroke Treatment (TOAST) classification was adopted to classify stroke etiology (Adams *et al* 1999). Symptomatic hemorrhage (sICH) was defined according to the definition of ECASS - European-Australian Cooperative Acute Stroke Study 3 (Hacke *et al* 2008).

The following data of included patients were collected: (1) demographic details (age, sex); (2) National Institutes of Health Stroke Scale (NIHSS) score at admission and on the 7th day or before in case of discharge; (3) premorbid mRS and mRS at discharge; (4) stroke risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, ischemic cardiopathy, atrial fibrillation); (5) Mortality; (6) length of hospitalization; (7) Non-enhanced CT (ASPECTscore) and Follow-up Non-enhanced CT; (8) Lesion side; (9) Intracerebral Hemorrage (ICH) and Symptomatic Intracerebral Hemorrage (sICH); (10) Stroke etiology by TOAST classification; (11) Stroke syndrome

by Bamford classification; (12) Endovascular treatment; (13) Time from last seen well to admission; (14) Time from symptom recognition to admission.

NECT and CTP acquisition and processing

CT standardized protocol at admission involved a non-enhanced CT, single-phase CT angiography and CTP. Follow-up imaging was performed with NECT at 22–36 hours after admission. All CT imaging was performed with 256-slices CT scanner (Brilliance iCT; Philips Medical Systems, Best, Netherlands). NECT was acquired with 120 kV, 400–450 mAs, at a slice thickness of 0.9 and reconstructed at 5 mm. CTP acquisition protocol involved injections of intravenous contrast medium administered at an injection rate of 4 ml/s and a total scanning time of 60 s. The exposure parameters used were 80 kVp and 150–200 mA s and a three-dimensional axial acquisition on the whole brain volume with a reconstruction of the slices set to 5 mm was performed.

CTP data processing was performed by using Extended Brilliance Workstation v 4.5 (Philips Medical Systems, Best, Netherlands) and a home-made code developed in Matlab (MathWorks Inc., Natick, MA), as previously described (Furlanis *et al* 2018, Stragapede *et al* 2019, Caruso *et al* 2019). Deconvolution-based method was used to calculate perfusion maps, namely mean transit time (MTT), cerebral blood volume (CBV) and cerebral blood flow (CBF). Models of the time/attenuation curves were obtained by curve fitting using least mean squares method, and the MTT map was subsequently calculated via a closed-form deconvolution operation using the time/concentration curve of a particular voxel and the arterial input function. For each voxel, the CBV map was calculated from the area under the time/concentration curves. CBF map was consequently calculated as a ratio between CBV and MTT. Ischemic penumbra and core areas were automatically identified by CTP maps processing identifying penumbra as voxels with MTT higher than 145% of the contralateral healthy area and CBV>2.0 ml/100g, while the infarcted core areas were identified as MTT>145% of the contralateral healthy area and CBV<2.0 ml/100g (Wintermark *et al* 2006).

To calculate the total ischemic volume excluding artifacts, CTP maps with hypoperfused voxels, representing both core and penumbra, were processed in 3D space with a semiautomatic algorithm as described in a previous study (Furlanis *et al* 2018). Algorithm is based on voxel connectivity using 26-connected neighborhoods for 3D images. Voxels belonging to the largest connected volume in 3D space, compatible with cerebral vascular territories area and clinical syndromes, were considered to calculate the total hypoperfused volume. The volume of core and penumbra

were calculated after the artefact removal by integration of identified core voxels and remaining hypoperfused penumbra area using aforementioned CBV thresholds. Ischemic Lesion Volume was calculated for all patients by a semi-automatic algorithm for segmentation, implemented in MATLAB (MathWorks, Natick, MA), based on seed-based region growing algorithm, and with the possibility of additional manual outlining. Two independent neurologists checked the results of this semiautomatic process.

Outcome measures

We have investigated the functional outcome in terms of the NIHSS determined at 7th day or at discharge before, as well as ΔNIHSS% calculated as percentage of NIHSS decreased from admission to discharge. Ischemic Lesion Volume at follow-up NECT and the percentage of reperfused tissue at 24 hours were also evaluated as a treatment efficacy outcome. The safety outcome was evaluated in terms of intrahospital mortality and sICH. The latter was defined as parenchymal hematoma type 2 (confluent blood clot occupying >30% of the infarct with substantial mass effect) within 36 hours after intervention, accompanied by an increase of at least 4 points in the NIHSS score from baseline (Hacke *et al* 2008).

Statistical analysis and mathematical modeling

We performed all statistical analysis using SPSS Statistics 23 (IBM, Armonk/NY, USA). Kolmogorov-Smirnov test was used to evaluate the normal distribution of variables. Continuous variables with a normal distribution are presented as mean and standard deviations (SDs), those with a skewed distribution as median and interquartile ranges (IQRs) indicating the 1st and 3rd quartile, and categorical variables as counts and percentages (%). To determine factors associated with NIHSS at 7 days and ischemic lesion volume calculated on follow-up NECT, multivariable linear regressions were performed. In particular, statistically significant variables at $p < 0.10$ at univariate analysis were selected as candidate factors for logistic and linear models. Results are presented as β, B and 95% confidence intervals (CI 95%). A value of $p < 0.05$ was considered significant.

A model to predict NIHSS at 7 days was developed by regularized least-squares regression using Least Absolute Shrinkage and Selection Operator (LASSO) method (Tibshirani 1994) as described in previous biomedical predictive modeling studies (Burke Quinlan *et al* 2015, Ajcevic *et al* 2015, 2016). The dataset was splitted into *training dataset*

used for parameter estimation and cross-validation and *testing dataset* was used to test the model on new unseen data. The *training dataset* consisted of 70% of the samples selected randomly, while the *testing dataset* consisted of the remaining 30% of the samples.

In this work, for the predictive estimation of NIHSS at 7 days we proposed an initial model which included the following features: CTP core volume, CTP penumbra volume, CTP total hypoperfused volume, CTP mismatch, Age, NHISS at baseline, premorbid mRS, time last seen well to admission and ASPECTS.

LASSO regression minimizes the cost function which consists of residual sum of squares (RSS) and of a regularization term (Tibshirani 1994):

$$\theta = argmin_{\theta} \left(RSS(\theta) + \lambda \sum_{j=1}^{p} |\theta_j| \right) \quad (1)$$

where θ is a parameter vector, p is number of coefficients and λ is a parameter which controls the model complexity. The regularization term prevents the coefficients of the model from having large absolute values, in order to avoid over-fitting. Thus, besides shrinking the linear model coefficients, this modeling approach also performs variable selection according to λ. For determined high values of λ, the coefficients of some variables are exactly zero, making the results highly interpretable (Tibshirani 1994). The λ parameter was chosen using 5-fold cross validation in order to minimize cross validation mean square error (Hastie *et al* 2009). In 5-fold cross-validation, the training dataset was partitioned into five equal sized subsamples. The four subsamples were used to train the model, while a remaining subsample was considered for the validation. The cross-validation process was then repeated five times, using each of the subsamples only once as the validation data. The 5-fold cross validation mean square error (MSE) and 95% CI were calculated. Subsequently, the produced model was applied on previously unseen testing dataset and MSE and 95% CI were calculated.

3. RESULTS

During the study period, 1172 (1059) patients with acute ischemic stroke were admitted to our Stroke Unit and 129 cases of them (11 %) suffered from WUS. As many as 83 out of 129 WUS patients were eligible and underwent rTPA, and were therefore included in the interventional rTPA group.

Patients' demographics and stroke characteristics

The baseline clinical and radiological characteristics, as well as risk factors of WUS patients, are presented in **Table 1**. Mean age was 74±13 years, and 59% of the sample were females. Median time from last seen well to admission was 527 min (375–712), and from symptom recognition to admission 98 min (64–127). Fifty-three percent of the sample suffered from an ischemic lesion on the left side of the brain, ASPECTS 10, and NIHSS 6 (4–13). Bamford stroke subtypes and TOAST classification are summarized in **Table 1**. CTP analysis suggested a mismatch value of 1.0 (0.9–1.0), a total volume of hypoperfused tissue of 13.4 mL (2.0–70.1), a penumbra volume of 13.3 mL (2.0–63.8), and core of 0 mL (0–3). The most predominant comorbidity were HTN (72%), dislipidemia (67%), and AF (30%). All included patients received rTPA treatment and 13 of them (16%) underwent EVT treatment.

Table 1: *Participants' demographics, clinical and radiological characteristics at baseline in rTPA treated (n= 83) wake up stroke patients. Data are presented as means±sd, medians (IQR) and frequencies.*

Personal Characteristics	**rTPA WUS n= 83**
Age [y]	74±13
Females [n (%)]	49 (59)
Last time seen well - Admission [min]	527 (375-712)
Symptom recognition -Admission [min]	98 (64-127)
ASPECTS	10 (10-10)
NIHSS at baseline	6 (4-13)
Anamnestic mRS	0 (0-0)
Left side of the lesion [n (%)]	44 (53)
Bamford stroke subtypes [n (%)]	
TACI	21 (25)
PACI	36 (43)
LACI	11 (13)
POCI	15 (18)
TOAST classification [n (%)]	
Atherothrombotic	19 (23)
Lacunar	10 (12)
Cardioembolic	25 (30)
Cryptogenic	29 (35)
Other cause	0 (0)
CTP parameters	
Mismatch	1.0 (0.9-1.0)
Total hypoperfused tissue [mL]	13.4 (2.0-70.1)
Penumbra [mL]	13.3 (2.0-63.8)
Core [mL]	0 (0-3)

HTN [n (%)]	60 (72)
DM [n (%)]	12 (15)
Dislipidemia [n (%)]	57 (67)
Smoking [n (%)]	19 (23)
Obesity [n (%)]	9 (11)
AF [n (%)]	25 (30)
ICP [n (%)]	17 (21)

Notes: Participants' reported age (y), sex (females, %), time between last time seen well and admission (min), time between stroke symptom recognition and admission (min), ASPECTS, NIHSS at baseline, anamnestic mRS, side of the ischemic lesion (left, %), Bamford stroke subtypes (%) (Total Anterior Circulation Infarct, TACI; Partial Anterior Circulation Infarct, PACI; Lacunar Stroke, LACI; Posterior Circulation Infarct, POCI), TOAST classification (%), CT Perfusion parameters (mL), history of hypertension (HTN, %), diabetes (DM, %), dislipidemia (%), smoking (%), obesity (%), atrial fibrillation (AF, %), ischemic cardiomyopathy (ICM, %).

Stroke Outcomes

Participants included in this sample were characterized by a NIHSS score at 7 days of 1 (0–4), with a percentage of NIHSS recovery of 75% (50–100%). Independence outcome at discharge, denoted by the mRS, suggested that 57% of the sample was characterized by a good outcome (mRS 0–2), and 45% by an "optimal" outcome (mRS 0–1). Follow-up NECT indicated a lesion volume of 1.0 mL (0-7-1.0 mL) and a percentage of reperfused tissue at 24 hours of 96% (68–100%). The proportion of patients with a reperfused tissue >50% at 24 hours was 87%, while patients with a reperfused tissue at 24 hours >90% were 57% of the sample. Median length of stay was 10 days (6–16 days). Intrahospital mortality was 6% of the sample, whereas ICH was found in 9% of the sample. Among those, 2% were sICH. Stroke outcomes are summarized in **Table 2**.

Table 2: *Clinical outcomes at 7 days and at discharge after admission in rTPA treated wake up stroke patients (n= 83). Data are presented as medians (IQR) and frequencies.*

Clinical Outcomes	**WUS rTPA n= 83**

NIHSS at 7 days	1 (0-4)
Δ NIHSS	4 (2-7)
Δ NIHSS percent	75 (50-100)
mRS at discharge 0-2 [n (%)]	47 (57)
mRS at discharge 0-1 [n (%)]	37 (45)
Final Ischemic Volume [mL]	1.0 (0.7-1.0)
Reperfused tissue 24h (%)	96 (68-100)
> 50%	74 (87)
> 90%	48 (57)
Length of Stay [days]	10 (6-16)
Mortality [n (%)]	5 (6)
ICH [n (%)]	11 (9)
sICH	2 (2)

Notes: Participants' NIHSS at 7 days from admission, difference between NIHSS at admission and NIHSS at 7 days (Δ NIHSS), percent of improvement between NIHSS at baseline and NIHSS at 7 days (Δ NIHSS percent), mRS between 0-2 (%) and 0-1 (%), final ischemic volume at follow-up NECT (mL), percentage of reperfused tissue at 24h as an absolute value (%) and proportion of patients with reperfused tissue > 50% and >90% [n (%)], length of intrahospital stay (days), mortality (%), intracerebral haemorrhage (ICH, %) and symptomatic cerebral haemorrhage (sICH, %). Results are summarized for all patients.

Factors Predictors of Good Outcomes

Univariate regression analysis suggested potential associations between NIHSS at 7 days and factors such as hypoperfused volume, core volume, NIHSS at baseline, anamnestic mRS, ASPECTS and TOAST classification. When these variables were included in the multivariate analysis, only core volume (β: 0.403, p= 0.000), NIHSS at baseline (β: 0.323, p= 0.005) and ASPECTS (β: -0.224, p= 0.012) remained significant predictors of NIHSS at 7 days (**Table 3**).

When ischemic lesion volume on follow up NECT was chosen as independent variable, hypoperfused volume, core volume, NIHSS at baseline, ASPECTS and TOAST classification were found associated in the univariate analysis. Nevertheless, the multivariate analysis showed that only total hypoperfused volume (β: 0.542, p= 0.000) and core volume (β: 0.441, p= 0.000) remained significant (**Table 4**). In our sample, the application of EVT treatment in addition to rTPA was not associated with the NIHSS at 7 days and final lesion volume.

Table 3*: Linear multivariate regression for NIHSS at 7 days after admission.*

Variable	β	B	NIHSS at 7 days 95% CI	Sig.
Hypoperfused volume (mL)	0.024	0.002	-0.018 – 0.022	0.846
Core volume (mL)	0.403	0.116	0.066 – 0.165	**0.000**
NIHSS at baseline	0.323	0.256	0.079 – 0.433	**0.005**
Anamnestic mRS	0.147	1.189	-0.115 – 2.494	0.073
ASPECTS	-0.224	-1.323	-2.349 – -0.298	**0.012**
TOAST classification	-0.019	-0.083	-0.771 –0.605	0.811

Notes: Multivariate analysis for NIHSS at 7 days from admission. Variables found significant in the univariate analysis. Hypoperfused volume (core + penumbra, mL), NIHSS at baseline, anamnestic mRS, ASPECTS, TOAST stroke classification. Significance (Sig.) for multivariate analysis. Bold values for $p < 0.05$.

Table 4*: Linear multivariate regression for final ischemic volume.*

Variable	β	B	Ischemic volume 95% CI	Sig.
Hypoperfused volume (mL)	0.542	0.363	0.224 – 0.502	**0.000**
Core volume (mL)	0.441	1.136	0.749 – 1.523	**0.000**
NIHSS at baseline	-0.114	-0.768	-2.141 – 0-604	0.268
ASPECTS	-0.113	-5.493	-12.877 – 1.891	0.143
TOAST classification	0.025	0.968	-4.428 – 6.364	0.722

Notes: Multivariate analysis for final ischemic volume (ischemic volume). Variables found significant in the univariate analysis. Hypoperfused volume (core + penumbra, mL), core volume (mL), NIHSS at baseline, ASPECTS, TOAST stroke classification. Significance (Sig.) for multivariate analysis. Bold values for $p < 0.05$.

Outcome Predictive Models

The identified model, represented by the following equation, was found for $\lambda=0.84$ and presented a 5-fold cross-validation MSE of 12.46 (95% CI 8.23 to 16.69) on the training dataset. The estimation mean square error MSE on

previously unseen testing dataset was 13.54 (95% CI 9.91 to 17.17), corresponding to root mean square error RMSE=3.68:

$$NIHSS_{7\ days} = 0.07 \cdot CTP_{core} + 0.01 \cdot CTP_{hypoperfused} + 0.22 \cdot NIHSS_{admission} - 0.89 \cdot ASPECTS + 8.89 \quad (2)$$

where CTP_{core} and $CTP_{hypoperfused}$ are volumes expressed in mL.

In **Figure 1**, the estimated values of NIHSS at 7 days obtained using the identified predictive model are plotted against the measured ones, on the training dataset (left panel) and test dataset (right panel) separately. The results showed dispersion around identity line between predicted and measured values. A slight underestimation trend was detected for higher NIHSS values.

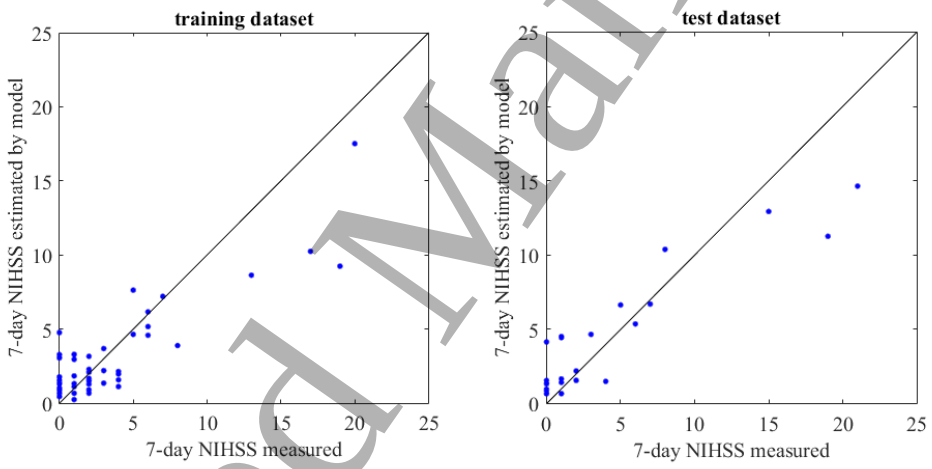

Figure 1. *Estimated values of NIHSS at 7 days obtained using the identified predictive model plotted against measured NIHSS at 7 days. (**Left panel**) training dataset; (**Right panel**) test dataset. The root mean square error observed on the test dataset was RMSE=3.68, R^2=0.81.*

4. DISCUSSION

There is growing research interest on CTP parameters which predicts the functional and morphological outcome in acute ischemic stroke patients. Currently there is little data about CTP calculated parameters predictivity for rTPA-treated WUS patients. The main finding of our study is the identification of CTP parameters, which, together with clinical data, can predict the outcome in terms of neurological deficit and final infarct volume in rtPA-treated WUS patients in everyday clinical scenario. This study also provides a simple model able to predict the 7 days NIHSS in

rTPA-treated WUS patients. In particular, CTP core volume together with NIHSS baseline and ASPECT score predict NIHSS at 7 days after admission, while hypoperfused volume and core volume at CTP predict infarct lesion volume at follow-up NECT. **Figure 2** and **Figure 3** respectively show two exemplificative cases of rTPA treated WUS patients reflecting the influence of different NIHSS, ASPECTS and infarct core at admission on functional and morphological outcomes.

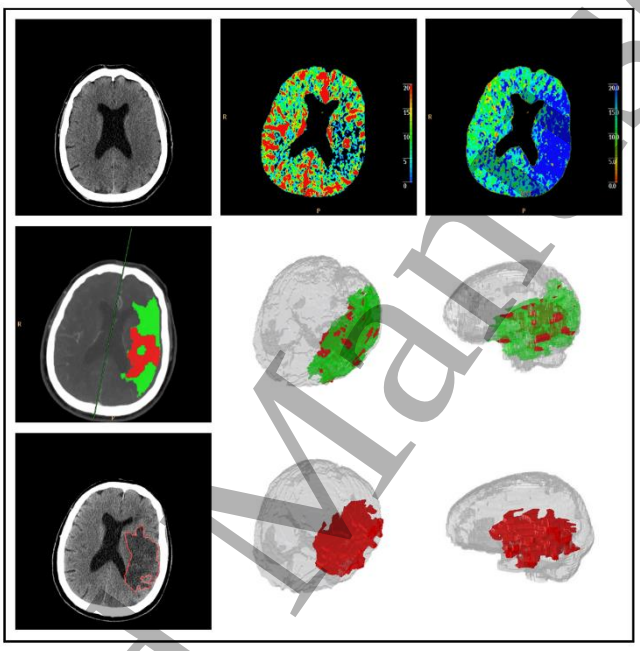

Figure 2. *rTPA treated wake-up stroke patient: female, 71 y, ASPECTS= 10, left M2- occlusion, NIHSS at admission= 17, premorbid mRS= 0, core volume= 0 mL; penumbra volume= 83.3 mL; total ischemic volume= 83.3 mL; NIHSS at 7 days= 2, mRS at discharge= 1; final ischemic volume= 3.6 mL.*

***Top Panel - From left to right**: NECT at admission, CBV and MTT - CTP calculated maps.*

***Middle Panel - From left to right:** CTP core-penumbra color map and its 3D reconstruction with estimated core area (145% of the contralateral healthy area and CBV <2.0 mL/ 100 g) and penumbra area (145% of the contralateral healthy area and CBV >2.0 mL/ 100 g), highlighted in red and green, respectively.*

***Bottom Panel - From left to right**: follow-up NECT, 3D reconstruction of ischemic lesion on follow-up NECT (red).*

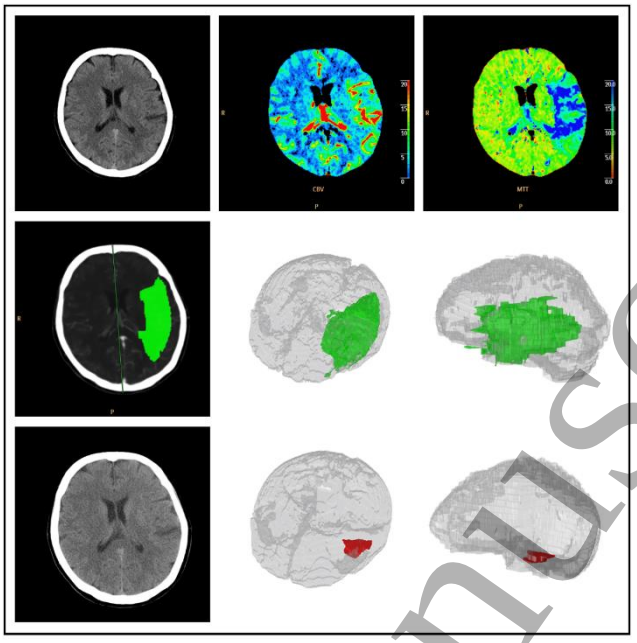

Figure 3. *rTPA treated wake-up stroke patient: male, 76 y, ASPECTS= 8, left M2- occlusion, NIHSS at admission= 24, premorbid mRS= 0, core volume= 41.7 mL; penumbra volume= 87.4 mL; total ischemic volume= 129.1 mL; NIHSS at 7 days= 19, mRS at discharge= 5; final ischemic volume= 83.6 mL.*

Top Panel - From left to right*: NECT at admission, CBV and MTT - CTP calculated maps.*

Middle Panel - From left to right: *CTP core-penumbra color map and its 3D reconstruction with estimated core area (145% of the contralateral healthy area and CBV <2.0 mL/ 100 g) and penumbra area (145% of the contralateral healthy area and CBV >2.0 mL/ 100 g), highlighted in red and green, respectively.*

Bottom Panel - From left to right*: follow-up NECT with delineated ischemic lesion, 3D reconstruction of ischemic lesion on follow-up NECT (red).*

Advanced neuroimaging, able to identify ischemic core and salvageable hypoperfused penumbra, is pivotal in decision-making of hyper-acute ischemic stroke and for patients' eligibility for treatment.(Vilela and Rowley 2017, Lewandowski and Libman 1999, Furlanis *et al* 2018, Caruso *et al* 2018, Furlanis *et al* 2019, Caruso *et al* 2019). Recent Trials based on MRI and CTP neuroimaging allowed the extension time window for endovascular treatment or rTPA therapy (Ma *et al* 2019, Nogueira *et al* 2018, Albers *et al* 2018) and demonstrated their safety and efficacy, also in WUS patients (Ma *et al* 2019, Thomalla *et al* 2018).

The results of WAKE UP trial showed the benefit of rTPA in WUS patients with DWI/FLAIR MRI pattern which indicated the stroke onset of less than 4.5 hours (Thomalla *et al* 2018). EXTEND trial, in which about 65% of included patients were WUS, by selecting cases with PWI/DWI MRI and CTP criteria, demonstrated that the rtPA resulted in higher number of patients with no or minor neurologic deficits (Ma *et al* 2019). A recent real-life study performed on 70 rTPA and mechanical thrombectomy treated patients admitted in an extended window beyond 4.5 hours from last seen well (60% of included patients were WUS) showed that reperfusion therapies were safe and effective in CTP selected patients (Feil *et al* 2019).

In our study the functional and morphological outcomes observed in rTPA treated WUS patients (mRS at discharge < 2 = 45%; sICH = 2%; median infarct volume at follow-up NECT= 1 mL; median percentage of reperfused tissue at 24h= 96%) are similar to those reported in the aforementioned trials. Our study focused on investigating the predictive power of calculated CTP parameters on final neurological deficit and infarct volume in rTPA-treated WUS patients. Our data showed that CTP core volume (β: 0.403, p= 0.000), NIHSS at baseline (β: 0.323, p= 0.005) and ASPECTS (β: -0.224, p= 0.012) are significant predictors of NIHSS at 7 days, while total CTP hypoperfused volume (β: 0.542, p= 0.000) and CTP core volume (β: 0.441, p= 0.000) are significant predictors of ischemic lesion volume on follow up NECT.

Recent studies investigated the CTP parameters predictivity in known onset ischemic stroke patients who underwent rTPA therapy or endovascular treatment (Agarwal *et al* 2011, Campbell *et al* 2019, Nogueira *et al* 2018, Albers *et al* 2018). Haranhalli et al. (2019) reported that in treated ischemic stroke the only baseline clinical characteristics that was significantly associated with worse mRS at discharge was NIHSS baseline > 16; at the same time CTP core volume was correlated with a worse functional outcome (Haranhalli *et al* 2019). Tian et al. (2019) showed that CTP assessed core was the only independent imaging CTP predictor of good functional outcome in rTPA treated patients with known onset of symptoms and admitted within 4.5 hours from onset (Tian *et al* 2019). Bivard et al. (2018) found that CTP infarct core volume and collateral grade are the strongest predictors of a good 3 months mRS outcome following rtPA treatment in patients admitted within 4.5 hours from ischemic symptom onset (Bivard *et al* 2018).

Time to rTPA treatment was also reported as weak predictor of outcome compared with CTP infarct core volume and collateral grade (Bivard *et al* 2018). Time last seen well to admission in our study was not associated with the clinical and morphological outcome. Our findings on CTP predictivity in WUS patients are consistent with those obtained in

known onset stroke (<4.5 hours) patients and support the hypothesis that the advanced imaging measures for patient treatment suitability may be even more important than the influence from time to treatment.

Furthermore, the results of our study showed that only total CTP hypoperfused volume and core volume are strong predictors of the final infarct volume in rTPA treated WUS patients. These results are consistent with studies on predictivity of CTP features on final infarct volume in known onset stroke patients (Shankar *et al* 2016, Padroni *et al* 2016). Shankar et al. (2016) found, investigating together treated and non-treated patients admitted <4.5 from onset, that CBV volumes assessed on CTP were the best predictor of final ischemic volume; at the same time, CBF volume was also correlated with the final lesion (Shankar *et al* 2016). In CTP ASPECTS study, Padroni et al. (2016) reported that CBF, CBV and MTT ASPECTS were inversely associated with final infarct volume, while CTP ASPECT mismatch was slightly associated with lesion considering treated and non-treated patients together (Padroni *et al* 2016).

Lastly, this study provides a simple predictive model to estimate the 7 days NIHSS in rTPA-treated WUS patients. The produced model presented root mean square error of 3.68 on previously unseen testing dataset indicating a good generalized estimation in our sample. The LASSO modeling approach confirmed the significant predictive power of CTP core volume, CTP total hypoperfused, NHISS at baseline and ASPECTS producing a sparse model eliminating age, CTP penumbra volume, CTP mismatch, premorbid mRS and time last seen well to admission features. Indeed, the selected features are related to *tissue clock* more that on *time clock*. CTP Infarct Core volume, ASPECT on NECT at admission and partially baseline NIHSS are related with irreversible necrotic brain injury (Wintermark *et al* 2006, Schramm *et al* 2004, Lin *et al* 2009, Campbell *et al* 2012, Hui *et al* 2017, Olive-Gadea *et al* 2019, Yaghi *et al* 2017, Payabvash *et al* 2017).

By attributing more importance to core related features, the results of our model support the hypothesis that the irreversible necrotic core, rather the extent of penumbra, is the main prognostic determinant in treated hyper-acute acute ischemic stroke patients. The importance of the core as outcome predictor in patients undergoing rTPA is underscored by studies using pretreatment MRI in patients with large vessel occlusion, showing that clinical outcome correlated significantly with lesion volume on diffusion-weighted imaging but not with the volume on perfusion/diffusion imaging mismatch (Nighoghossian *et al* 2003). Although slightly, the total ischemic CTP volume

participates to the final neurological deficit directly and also through its contribution to NIHSS at admission (Furlanis *et al* 2018).

Our study has, however, some limitations. The data describe a single-center investigation of a limited sample size. Moreover, although the included patients were consecutive, we conducted an observational study. Our study population represents only mild/moderate stroke severity with a median NIHSS score at baseline 6 and with significant prevalence penumbra compared to ischemic core. The produced predictive model should be considered bearing in mind the aforementioned dataset limitations. As the follow-up at 3 months is not mandatory, mRS was collected at discharge. The results should be confirmed and the model should be refined in a larger sample. Despite these limitations, this study contributes to give a better insight on the predictive power of whole brain CTP features and clinical stroke related parameters on functional and morphological outcome of rTPA-treated WUS patients in real-life clinical scenario.

In conclusion, the results of our study show that CTP core volume together with NIHSS baseline and ASPECT score predict NIHSS at 7 days after admission, while hypoperfused volume and core volume at CTP predict infarct lesion volume at follow-up NECT in rTPA treated WUS patients. These findings support the importance of features extracted from CT multimodal imaging in the decision-making and predictivity in the hyperacute phase of wake-up ischemic stroke. The study also provides a predictive model to estimate neurologic deficit at 7 days that, by attributing importance to core related features strengthens the hypothesis that irreversible necrotic core, rather the extent of penumbra, is the main prognostic determinant in treated hyper-acute ischemic stroke patients.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Compliance with Ethical Standards

The authors declare no conflicts of interest for present study. The research was conducted according to the principles of the Declaration of Helsinki. All participants released their informed consent for treatment of clinical data after all procedures had been fully explained, as for standard institutional procedure. This retrospective study was approved by the Local Ethics Committee CEUR (Comitato Etico Unico Regionale, FVG, Italy) with approval number 115/2018.

References

Adams H P J, Davis P H, Leira E C, Chang K C, Bendixen B H, Clarke W R, Woolson R F and Hansen M D 1999 Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology* **53** 126–31

Agarwal S, Jones P S, Alawneh J A, Antoun N M, Barry P J, Carrera E, Cotter P E, O'Brien E W, Salih I, Scoffings D J, Baron J-C and Warburton E A 2011 Does perfusion computed tomography facilitate clinical decision making for thrombolysis in unselected acute patients with suspected ischaemic stroke? *Cerebrovasc. Dis.* **32** 227–33

Ajcevic M, Lucangelo U and Accardo A 2015 Estimation of the difference between peak airway and tracheal pressures during HFPV *23rd European Signal Processing Conference (EUSIPCO)* pp 2566–70

Ajcevic M, Lucangelo U and Accardo A 2016 Estimation of the Endotracheal Tube Pressure Drop during HFPV: A Flow-Independent Model *XIV Mediterranean Conference on Medical and Biological Engineering and Computing 2016* pp 129–33

Albers G W, Marks M P, Kemp S, Christensen S, Tsai J P, Ortega-Gutierrez S, McTaggart R A, Torbey M T, Kim-Tenser M, Leslie-Mazwi T, Sarraj A, Kasner S E, Ansari S A, Yeatts S D, Hamilton S, Mlynash M, Heit J J, Zaharchuk G, Kim S, Carrozzella J, Palesch Y Y, Demchuk A M, Bammer R, Lavori P W, Broderick J P and Lansberg M G 2018 Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. *N. Engl. J. Med.* **378** 708–18

Barreto A D, Fanale C V., Alexandrov A V., Gaffney K C, Vahidy F S, Nguyen C B, Sarraj A, Rahbar M, Grotta J C, Savitz S I and Wake-Up Stroke Investigators 2016 Prospective, open-label safety study of intravenous recombinant tissue plasminogen activator in wake-up stroke *Ann. Neurol.* **80** 211–8

Bivard A, Spratt N, Miteff F, Levi C and Parsons M W 2018 Tissue Is More Important than Time in Stroke Patients Being Assessed for Thrombolysis. *Front. Neurol.* **9** 41

Burke Quinlan E, Dodakian L, See J, McKenzie A, Le V, Wojnowicz M, Shahbaba B and Cramer S C 2015 Neural

function, injury, and stroke subtype predict treatment gains after stroke. *Ann. Neurol.* **77** 132–45

Campbell B C V, Christensen S, Levi C R, Desmond P M, Donnan G A, Davis S M and Parsons M W 2012 Comparison of computed tomography perfusion and magnetic resonance imaging perfusion-diffusion mismatch in ischemic stroke. *Stroke* **43** 2648–53

Campbell B C V, Ma H, Ringleb P A, Parsons M W, Churilov L, Bendszus M, Levi C R, Hsu C, Kleinig T J, Fatar M, Leys D, Molina C, Wijeratne T, Curtze S, Dewey H M, Barber P A, Butcher K S, De Silva D A, Bladin C F, Yassi N, Pfaff J A R, Sharma G, Bivard A, Desmond P M, Schwab S, Schellinger P D, Yan B, Mitchell P J, Serena J, Toni D, Thijs V, Hacke W, Davis S M and Donnan G A 2019 Extending thrombolysis to 4.5-9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. *Lancet (London, England)*

Caruso P, Furlanis G, Ridolfi M, Ajcevic M, Naccarato M and Manganotti P 2019 Safety of Early Repeated Thrombolysis A Case Report *Neurologist* **24** 143–5

Caruso P, Naccarato M, Furlanis G, Ajcevic M, Stragapede L, Ridolfi M, Polverino P, Ukmar M and Manganotti P 2018 Wake-up stroke and CT perfusion: effectiveness and safety of reperfusion therapy. *Neurol. Sci. Off. J. Ital. Neurol. Soc. Ital. Soc. Clin. Neurophysiol.* **39** 1705–12

Denny MC, Boehme AK, Dorsey AM, George AJ, Yeh AD, Albright KC et al 2014 Wake-up strokes are similar to known-onset morning strokes in severity and outcome. *J Neurol Neurol Disord 2014* 1:pii: 102.

Etherton M R, Barreto A D, Schwamm L H and Wu O 2018 Neuroimaging Paradigms to Identify Patients for Reperfusion Therapy in Stroke of Unknown Onset. *Front. Neurol.* **9** 327

Feil K, Reidler P, Kunz W G, Kupper C, Heinrich J, Laub C, Muller K, Voglein J, Liebig T, Dieterich M and Kellert L 2019 Addressing a real-life problem: treatment with intravenous thrombolysis and mechanical thrombectomy in acute stroke patients with an extended time window beyond 4.5 h based on computed tomography perfusion imaging. *Eur. J. Neurol.*

Furlanis G, Ajcevic M, Buoite Stella A, Cillotto T, Caruso P, Ridolfi M, Cova M A, Naccarato M and Manganotti P 2019 Wake-up stroke: thrombolysis reduces ischemic lesion volume and neurological deficit *J. Neurol.* in

press

Furlanis G, Ajcevic M, Stragapede L, Lugnan C, Ridolfi M, Caruso P, Naccarato M, Ukmar M and Manganotti P 2018 Ischemic Volume and Neurological Deficit: Correlation of Computed Tomography Perfusion with the National Institutes of Health Stroke Scale Score in Acute Ischemic Stroke. *J. Stroke Cerebrovasc. Dis.* **27** 2200–7

Gonzalez R G 2006 Imaging-guided acute ischemic stroke therapy: From "time is brain" to "physiology is brain". *AJNR. Am. J. Neuroradiol.* **27** 728–35

Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, Larrue V, Lees K R, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N and Toni D 2008 Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N. Engl. J. Med.* **359** 1317–29

Haranhalli N, Mbabuike N, Grewal S S, Hasan T F, Heckman M G, Freeman W D, Gupta V, Vibhute P, Brown B L, Miller D A, Jahromi B S and Tawk R G 2019 Topographic correlation of infarct area on CT perfusion with functional outcome in acute ischemic stroke. *J. Neurosurg.* 1–9

Hastie T, Tibshirani R and Friedman J 2009 *The elements of statistical learning: data mining, inference, and prediction* (Berlin: Springer)

Hui F K, Obuchowski N A, John S, Toth G, Katzan I, Wisco D, Cheng-Ching E, Uchino K, Man S-M and Hussain S 2017 ASPECTS discrepancies between CT and MR imaging: analysis and implications for triage protocols in acute ischemic stroke. *J. Neurointerv. Surg.* **9** 240–3

Kang D-W, Sohn S-I, Hong K-S, Yu K-H, Hwang Y-H, Han M-K, Lee J, Park J-M, Cho A-H, Kim H-J, Kim D-E, Cho Y-J, Koo J, Yun S-C, Kwon S U, Bae H-J and Kim J S 2012 Reperfusion Therapy in Unclear-Onset Stroke Based on MRI Evaluation (RESTORE) *Stroke* **43** 3278–83

Kawano H, Bivard A, Lin L, Ma H, Cheng X, Aviv R, O'Brien B, Butcher K, Lou M, Zhang J, Jannes J, Dong Q, Levi C R and Parsons M W 2017 Perfusion computed tomography in patients with stroke thrombolysis. *Brain* **140** 684–91

Lewandowski C A and Libman R 1999 Acute presentation of stroke. *J. Stroke Cerebrovasc. Dis.* **8** 117–26

Lin K, Do K G, Ong P, Shapiro M, Babb J S, Siller K A and Pramanik B K 2009 Perfusion CT improves diagnostic accuracy for hyperacute ischemic stroke in the 3-hour window: study of 100 patients with diffusion MRI confirmation. *Cerebrovasc. Dis.* **28** 72–9

Ma H, Campbell B C V, Parsons M W, Churilov L, Levi C R, Hsu C, Kleinig T J, Wijeratne T, Curtze S, Dewey H M, Miteff F, Tsai C-H, Lee J-T, Phan T G, Mahant N, Sun M-C, Krause M, Sturm J, Grimley R, Chen C-H, Hu C-J, Wong A A, Field D, Sun Y, Barber P A, Sabet A, Jannes J, Jeng J-S, Clissold B, Markus R, Lin C-H, Lien L-M, Bladin C F, Christensen S, Yassi N, Sharma G, Bivard A, Desmond P M, Yan B, Mitchell P J, Thijs V, Carey L, Meretoja A, Davis S M and Donnan G A 2019 Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke *N. Engl. J. Med.* **380** 1795–803

Mackey J, Kleindorfer D, Sucharew H, Moomaw C J, Kissela B M, Alwell K, Flaherty M L, Woo D, Khatri P, Adeoye O, Ferioli S, Khoury J C, Hornung R and Broderick J P 2011 Population-based study of wake-up strokes *Neurology* **76** 1662–7

Manganotti P, Furlanis G, Ajčević M, Polverino P, Caruso P, Ridolfi M, Pozzi-Mucelli R A, Cova M A and Naccarato M 2019 CT perfusion and EEG patterns in patients with acute isolated aphasia in seizure-related stroke mimics *Seizure - Eur. J. Epilepsy* **71** 110–5 Online: https://doi.org/10.1016/j.seizure.2019.07.005

Nighoghossian N, Hermier M, Adeleine P, Derex L, Dugor J F, Philippeau F, Ylmaz H, Honnorat J, Dardel P, Berthezene Y, Froment J C and Trouillas P 2003 Baseline magnetic resonance imaging parameters and stroke outcome in patients treated by intravenous tissue plasminogen activator. *Stroke* **34** 458–63

Nogueira R G, Jadhav A P, Haussen D C, Bonafe A, Budzik R F, Bhuva P, Yavagal D R, Ribo M, Cognard C, Hanel R A, Sila C A, Hassan A E, Millan M, Levy E I, Mitchell P, Chen M, English J D, Shah Q A, Silver F L, Pereira V M, Mehta B P, Baxter B W, Abraham M G, Cardona P, Veznedaroglu E, Hellinger F R, Feng L, Kirmani J F, Lopes D K, Jankowitz B T, Frankel M R, Costalat V, Vora N A, Yoo A J, Malik A M, Furlan A J, Rubiera M, Aghaebrahim A, Olivot J-M, Tekle W G, Shields R, Graves T, Lewis R J, Smith W S, Liebeskind D S, Saver J L and Jovin T G 2018 Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. *N. Engl. J. Med.* **378** 11–21

Olive-Gadea M, Martins N, Boned S, Carvajal J, Moreno M J, Muchada M, Molina C A, Tomasello A, Ribo M and Rubiera M 2019 Baseline ASPECTS and e-ASPECTS Correlation with Infarct Volume and Functional Outcome in Patients Undergoing Mechanical Thrombectomy. *J. neuroimaging* **29** 198–202

Padroni M, Bernardoni A, Tamborino C, Roversi G, Borrelli M, Saletti A, De Vito A, Azzini C, Borgatti L, Marcello O, d'Esterre C, Ceruti S, Casetta I, Lee T-Y and Fainardi E 2016 Cerebral Blood Volume ASPECTS Is the Best Predictor of Clinical Outcome in Acute Ischemic Stroke: A Retrospective, Combined Semi-Quantitative and Quantitative Assessment. *PLoS One* **11** e0147910

Payabvash S, Taleb S, Benson J C and McKinney A M 2017 Acute Ischemic Stroke Infarct Topology: Association with Lesion Volume and Severity of Symptoms at Admission and Discharge. *AJNR. Am. J. Neuroradiol.* **38** 58–63

Powers W J, Rabinstein A A, Ackerson T, Adeoye O M, Bambakidis N C, Becker K, Biller J, Brown M, Demaerschalk B M, Hoh B, Jauch E C, Kidwell C S, Leslie-Mazwi T M, Ovbiagele B, Scott P A, Sheth K N, Southerland A M, Summers D V and Tirschwell D L 2018 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* **49** e46–110

Rubin M N and Barrett K M 2015 What to do With Wake-Up Stroke *The Neurohospitalist* **5** 161–72

Ryu W H A, Avery M B, Dharampal N, Allen I E and Hetts S W 2017 Utility of perfusion imaging in acute stroke treatment: a systematic review and meta-analysis. *J. Neurointerv. Surg.* **9** 1012–6

Schramm P, Schellinger P D, Klotz E, Kallenberg K, Fiebach J B, Kulkens S, Heiland S, Knauth M and Sartor K 2004 Comparison of perfusion computed tomography and computed tomography angiography source images with perfusion-weighted imaging and diffusion-weighted imaging in patients with acute stroke of less than 6 hours' duration. *Stroke* **35** 1652–8

Shankar J J S, Langlands G, Doucette S and Phillips S 2016 CT Perfusion in Acute Stroke Predicts Final Infarct Volume- Inter-observer Study. *Can. J. Neurol. Sci.* **43** 93–7

Stragapede L, Furlanis G, Ajcevic M, Ridolfi M, Caruso P, Naccarato M, Ukmar M and Manganotti P 2019 Brain

oscillatory activity and CT perfusion in hyper-acute ischemic stroke. *J. Clin. Neurosci.* pii: S0967-5868(19)30948-8

Thomalla G, Fiebach J B, Ostergaard L, Pedraza S, Thijs V, Nighoghossian N, Roy P, Muir K W, Ebinger M, Cheng B, Galinovic I, Cho T-H, Puig J, Boutitie F, Simonsen C Z, Endres M, Fiehler J and Gerloff C 2014 A multicenter, randomized, double-blind, placebo-controlled trial to test efficacy and safety of magnetic resonance imaging-based thrombolysis in wake-up stroke (WAKE-UP). *Int. J. stroke* **9** 829–36

Thomalla G, Simonsen C Z, Boutitie F, Andersen G, Berthezene Y, Cheng B, Cheripelli B, Cho T-H, Fazekas F, Fiehler J, Ford I, Galinovic I, Gellissen S, Golsari A, Gregori J, Gunther M, Guibernau J, Hausler K G, Hennerici M, Kemmling A, Marstrand J, Modrau B, Neeb L, Perez de la Ossa N, Puig J, Ringleb P, Roy P, Scheel E, Schonewille W, Serena J, Sunaert S, Villringer K, Wouters A, Thijs V, Ebinger M, Endres M, Fiebach J B, Lemmens R, Muir K W, Nighoghossian N, Pedraza S and Gerloff C 2018 MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. *N. Engl. J. Med.* **379** 611–22

Tian H, Parsons M W, Levi C R, Lin L, Aviv R I, Spratt N J, Butcher K S, Lou M, Kleinig T J and Bivard A 2019 Influence of occlusion site and baseline ischemic core on outcome in patients with ischemic stroke. *Neurology* **92** e2626–43

Tibshirani R 1994 Regression shrinkage and selection via the Lasso *J. R. Stat. Soc.* **58** 267288

Vilela P and Rowley H A 2017 Brain ischemia: CT and MRI techniques in acute ischemic stroke. *Eur. J. Radiol.* **96** 162–72

Wintermark M, Flanders A E, Velthuis B, Meuli R, van Leeuwen M, Goldsher D, Pineda C, Serena J, van der Schaaf I, Waaijer A, Anderson J, Nesbit G, Gabriely I, Medina V, Quiles A, Pohlman S, Quist M, Schnyder P, Bogousslavsky J, Dillon W P and Pedraza S 2006 Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. *Stroke* **37** 979–85

Yaghi S, Herber C, Boehme A K, Andrews H, Willey J Z, Rostanski S K, Siket M, Jayaraman M V, McTaggart R A, Furie K L, Marshall R S, Lazar R M and Boden-Albala B 2017 The Association between Diffusion MRI-

Defined Infarct Volume and NIHSS Score in Patients with Minor Acute Stroke. *J. neuroimaging* **27** 388–91