Available online at www.sciencedirect.com

ScienceDirect

Procedia Computer Science 192 (2021) 2919–2925

Procedia Computer Science

www.elsevier.com/locate/procedia

25th International Conference on Knowledge-Based and Intelligent Information & Engineering Systems

Ischemic lesion volume prediction in thrombolysis treated wake-up stroke patients

Miloš Ajčević[a,*], Aleksandar Miladinović[a,b], Giovanni Furlanis[c], Marcello Naccarato[c], Alex Buoite Stella[c], Paola Caruso[c], Paolo Manganotti[c] and Agostino Accardo[a]

[a]*Department of Engineering and Architecture, University of Trieste, 34127 Trieste, Italy*
[b]*Institute for Maternal and Child Health – IRCCS, Burlo Garofolo, Trieste, 34137, Italy*
[c]*Neurology Unit, Trieste University Hospital, Department of Medicine Surgery and Health Sciences, University of Trieste, 34137 Trieste, Italy*

Abstract

There is growing research interest on identification of CT Perfusion (CTP) parameters that predict the outcome in acute ischemic stroke patients. The aim of this study is to produce the model, based on core-penumbra related parameters assessed by CTP processing and commonly used clinical prediction factors, to predict the final infarct volume in thrombolysis-treated anterior circulation wake-up stroke (WUS) patients. The study was conducted on 51 consecutive wake-up ischemic stroke patients. The model for the predictive estimation of final ischemic volume was determined by using the Least Absolute Shrinkage and Selection Operator (LASSO) regularized least-squares regression. The results showed that CTP core volume and CTP total ischemic volume at admission, together with ASPECT score predict the final infarct lesion volume. In particular, the identified model presented 5-fold cross-validation root mean square error RMSE of 8.1 ml and the coefficient of determination (R^2=0.94) on our dataset. The results should be confirmed in a lager study. In conclusion, in this study we preliminarily identified a predictive model to estimate final ischemic lesion volume in thrombolysis treated wake-up stroke patients.

Keywords: Wake-up stroke; Predictive modeling; Ischemic lesion volume; CT Perfusion; Neuroimaging.

* Corresponding author. Tel.: +39-0405587120; fax: +39-0405583460.
E-mail address: majcevic@units.it

10.1016/j.procs.2021.09.063

1. Introduction

Ischemic stroke, which is caused by blockage of a blood vessel, is still one of the principal causes of disability and mortality worldwide, despite advances in disease prevention and acute treatment [1]. This neuroemergency condition currently is highly treatable using thrombectomy and intravenous thrombolysis in selected patients [2]. Thrombolysis is widely adopted to perform to facilitate reperfusion in patients with acute ischemic stroke and its benefits are well established [2], [3], also in wake-up stroke (WUS) patients [4]. Wake-up Stroke represents around a quarter of acute ischemic stroke events [5].

Early post-stroke prognosis is important for guiding treatment and rehabilitation strategies, in order to improve recovery and minimize disability. Different demographic, clinical and neuroimaging factors were associated with functional outcome. Early prediction of post-stroke outcome is still challenging since there is large inter-subject variability. The functional outcome is highly related to the final extent of the ischemic infarct [6-8], although this is of course also dependent on lesion location.

Neuroimaging has been proving to be pivotal in ischemic stroke diagnosis and it is of paramount importance for patients' eligibility for treatment [9]. CT Perfusion (CTP) technology allows fast assessment of the extent ischemic core and salvageable hypoperfused penumbra area and is increasingly adopted in emergency setting [10], [11]. CTP provides good diagnostic accuracy in the identification of acute ischemic stroke [12-14] allowing the identification of patients eligible for the reperfusion treatment [11], also in cases of wake-up stroke [4].

There is growing research interest on identification of CTP parameters which predict the functional and morphological outcome in acute ischemic stroke patients. A recent study showed that total CTP hypoperfused volume and core volume are strong independent predictors of the final infarct volume in thrombolysis-treated WUS patients [15]. The aim of this preliminary study is to produce the model, based on core-penumbra related parameters assessed by CTP processing and commonly used clinical prediction factors, to predict the final infarct volume in thrombolysis-treated anterior circulation WUS patients.

Nomenclature

ASPECTS	Alberta Stroke Programme Early CT Score
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CTP	CT Perfusion
LASSO	Least Absolute Shrinkage and Selection Operator
mRS	Modified Rankin Score
MTT	Mean Transit Time
NECT	Non-Enhanced CT
NIHSS	National Institutes of Health Stroke Scale
RMSE	Root Mean Square Error
rtPA	Recombinant Tissue Plasminogen Activator
WUS	Wake-up Stroke

2. Materials and methods

2.1. Study population and protocol

The study was conducted on 51 consecutive wake-up stroke patients (23 M/28 F; age 74±12 years) admitted to the Stroke Unit of the Trieste University Hospital, Italy. Patients with acute ischemic stroke developed at morning awakening who underwent CTP assessment and reperfusion treatment, and admitted within 4.5 hours from awakening were included. Both genders were included in the study sample and no age limit was applied. Exclusion

criteria were hemorrhagic stroke and previous brain lesion. Due to lower sensibility of CTP, patients with posterior circulation stroke were also excluded [16]. Stroke mimics were excluded by a complete diagnostic work-up including clinical and CT or MRI follow-up assessment.

Non-enhanced CT (NECT), Angio-CT, CT Perfusion at admission and a follow-up NECT were performed in all included patients. 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). The following data were collected for each included patient: demographic data (age, sex); NIHSS score at admission [17]; pre-morbid mRS [18]; ASPECT score at admission NECT [19]; Time from last seen well to admission; CTP scans at admission and follow-up NECT.

The research was conducted according to the ethical principles of the Declaration of Helsinki. All participants provided their informed consent. This study was approved by the Regional Ethical Committee (Comitato Etico Unico Regionale - CEUR, Friuli Venezia Giulia, Italy).

2.2. CT acquisition and processing

CT imaging was performed with 256-slices CT scanner (Brilliance iCT; Philips Medical Systems, Best, Netherlands). At initiation of scanning, 75 ml of contrast medium was injected intravenously at a rate of 4 ml/s, followed by a 40 ml of saline bolus. The three-dimensional axial acquisitions on a whole brain volume with a reconstruction of the slices set to 5 mm were performed. The acquisitions were carried out every 4 s, resulting in a total scanning time of 60 s. CTP source image processing was performed by Extended Brilliance Workstation v 4.5 (Philips Medical Systems, Best, Netherlands) and in-house developed in Matlab (MathWorks Inc., Natick, MA), as previously described [12-15]. CTP analysis is summarized in Figure 1. The perfusion maps mean transit time (MTT), cerebral blood volume (CBV) and cerebral blood flow (CBF) were calculated from source CTP. Gaussian curve fitting by least mean squares method was applied to obtain mathematical descriptions of the time-density curves for each voxel. An arterial input function and venous output are selected and subsequently a closed-form deconvolution was applied to produce a MTT maps. CBV map was calculated from the area under the time attenuation curve and finally CBF map as a ratio between CBV and MTT. Ischemic core and penumbra areas were identified by application of specific thresholds [17], i.e. MTT voxels >145% of the contralateral healthy area and CBV<2.0 mL/100 g, and MTT voxels > 145% of the contra-lateral healthy area and CBV>2.0 mL/100 g, respectively. Total ischemic volume (core + penumbra) excluding artifacts was calculated by integration of identified voxels as described in a previous study [12].

Final ischemic volume was segmented on follow-up NECT by using a seed-based region growing algorithm implemented in Matlab (MathWorks Inc., Natick, MA) and additionally manually outlined by two trained neurologists.

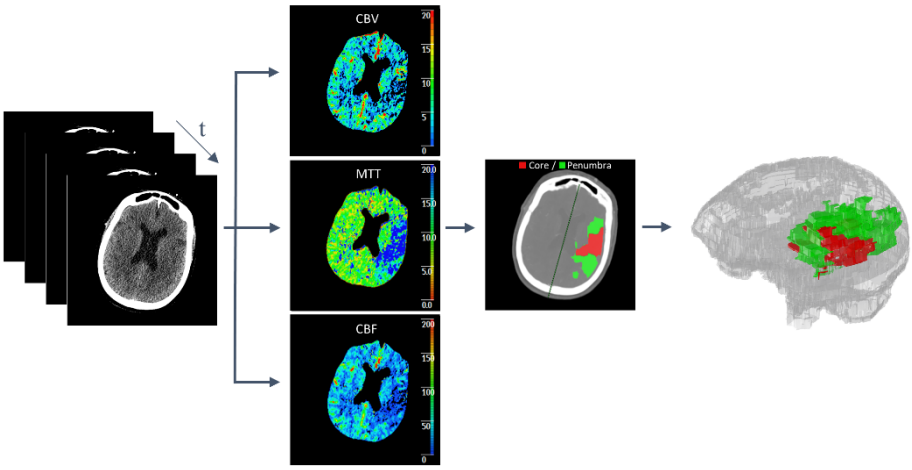

Fig. 1. Summary of CT Perfusion (CTP) analysis. From left to right: source CTP data; CBV, MTT and CBF calculated maps, from top to bottom, respectively; core (red) - penumbra (green) thresholded map; 3D representation of core, penumbra and total hypoperfused volume (core + penumbra).

2.3. Predictive modeling

A model to predict the final extent of ischemic lesion was developed by regularized least-squares regression using Least Absolute Shrinkage and Selection Operator (LASSO) method [21]. In this study, for the predictive estimation of final ischemic volume ($Vol_{lession}$) we proposed an initial model which included the CTP core-penumbra features and commonly used clinical prediction factors. In particular, the initial model included: CTP core volume (CTP_{core}), CTP total hypoperfused volume ($CTP_{hypoperfused}$), *NHISS* at admission, *ASPECTS*, Age, premorbid *mRS* and time from last seen well to admission. LASSO regression minimizes the cost function which consists of residual sum of squares (RSS) and of a regularization term [21]:

$$\vartheta = \arg\min_{\vartheta}(RSS(\vartheta) + \lambda \sum_{j=1}^{p} |\vartheta_j| \tag{1}$$

where θ is a parameter vector of all coefficients, p is number of coefficients (p = 7) 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 overfitting. Thus, besides shrinking the linear model coefficients, this modeling approach also performs variable selection according to λ. For determined relatively high values of λ, the coefficients of less predictive variables are approaching zeros, producing a sparse model and making the results easily interpretable [21]. The λ parameter was chosen using 5-fold cross validation in order to minimize cross validation mean square error [22].

3. Results

Fifty-one patients (23 M/28 F; age 74±12 years) were included in the study. Patient's demographic and clinical data at admission, as well as neuroimaging findings are summarized in Table 1. Median NIHSS score at admission was 7 (1 - 30) while median pre-morbid mRS was 0 (0 - 3). ASPECT score assessed on NECT was 10 (7 - 10). Median Core volume calculated on CTP was 0.0 ml (0.0 – 147.5), while median total ischemic volume calculated on CTP was 7.9 ml (2.5 – 280.0).

Table 1. Clinical characteristics and neuroimaging findings at admission.

Age (mean±1SD)	74 ± 12 years
Gender M:F	23 : 28
Last time seen well to Admission (median, range)	556 (341-1273) min
ASPECT score (median, range)	10 (7 - 10)
NIHSS admission (median, range)	7 (1 - 30)
Pre-morbid mRS (median, range)	0 (0 - 3)
Ischemic core volume (median, range)	0.0 (0.0 - 147.5) ml
Total ischemic volume (median, range)	7.9 (2.5 – 280.0) ml

The identified model, represented by following equation, was found for λ=0.79:

$$Vol_{lession} = 1.03 \cdot CTP_{core} + 0.23 \cdot CTP_{hyporfused} - 2.21 \cdot ASPECTS + 22.14 \quad (2)$$

The model presented 5-fold cross-validation root mean square error RMSE of 8.1 ml and the coefficient of determination (R^2=0.94). In Figure 2, the estimated values of final ischemic lesion volume obtained using the identified predictive model are plotted against the measured ones, for all subjects. The results showed dispersion around identity line between predicted and measured values. A slight underestimation trend was observed for higher values.

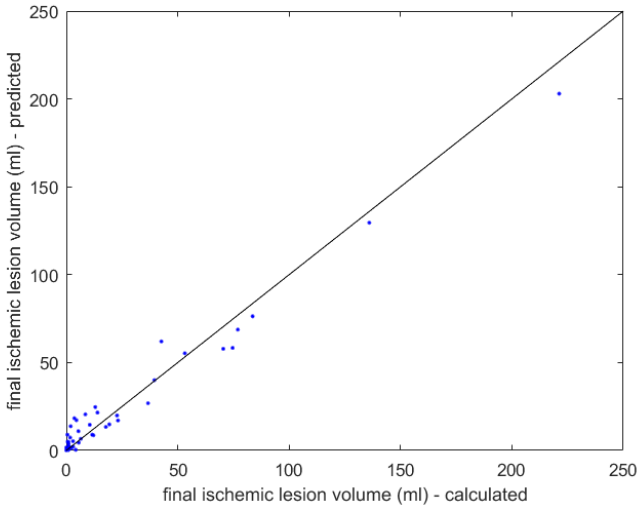

Fig. 2. Estimated values of final ischemic lesion volume obtained using the identified predictive model plotted against measured ones.

4. Discussion

The identification of individual factors modulating recovery after a stroke is important to personalize the therapeutic intervention and to improve the final functional outcome. The early prediction of stroke functional and

morphological outcome still represents one of the main focuses of stroke related research. Stroke outcome in treated patents was found to be related to early alterations of neurophysiological parameters, such as EEG spectral parameters [23] and CT Perfusion parameters [24], [25]. In particular, recent studies investigated the CTP parameters predictivity in known onset ischemic stroke patients who underwent thrombolysis therapy or endovascular treatment [24], [25]. However, only a few studies focused on final infract volume, especially in case of thrombolysis-treated WUS patients.

The main finding of our study is the identification of the model, based on CT Perfusion core-penumbra parameters and clinical data, which can predict the final ischemic lesion volume in thrombolysis-treated WUS patients. In particular, CTP core volume, and CTP total ischemic volume at admission, together with ASPECT score predict the final infarct lesion volume at assessed on follow-up NECT.

Our findings are consistent with studies on predictivity of CTP features on final infarct volume in known onset stroke patients [26, 27]. Shankar et al. 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 [26].

In CTP ASPECTS study, Padroni et al. 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 [27]. In our study LASSO modeling approach confirmed the significant predictive power of CTP core volume, CTP total hypoperfused volume and ASPECT score producing a sparse model eliminating age, NIHSS at admission, 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 are related with irreversible necrotic brain injury [20], [28]. 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.

Our study has some limitations. Beside a limited sample size, our study population represent mainly mild/moderate stroke severity, with a significant prevalence penumbra compared to ischemic core. Thus, the results should be confirmed in a lager study and the produced predictive model should be considered taking into account the aforementioned dataset limitations.

In conclusion, in this study we preliminarily identified a predictive model to estimate final ischemic lesion volume in thrombolysis treated wake-up stroke patients.

Acknowledgements

This study was partially supported by Master in Clinical Engineering, University of Trieste.

Conflict of interest

The authors have no conflict of interest do declare.

References

[1] Gorelick, P. B.: The global burden of stroke: persistent and disabling. The Lancet Neurology 18(5), 417–418 (2019).

[2] The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group: Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 333, 1581–1587 (1995).

[3] Puetz, V., Barlinn, K., Bodechteil, E., et al.: Imaging-based selection for revascularization in acute ischemic stroke. Current opinion in neurology 29, 20–29 (2016).

[4] Furlanis, G., Ajčević, M., Buoite Stella, A., et al.: Wake-up stroke: thrombolysis reduces ischemic lesion volume and neurological deficit. Journal of neurology 267(3), 666–673 (2020).

[5] Mackey, J., Kleindorfer, D., Sucharew, H., et al.: Population-based study of wake-up strokes. Neurology 76, 1662–1667 (2011).

[6] Jacobs, M. A., Mitsias, P. D., Soltanian-Zadeh, H., et al.: Multiparametric MRI tissue characterization in clinical stroke with correlation to clinical outcome: part 2. Stroke 32, 950–957 (2001).

[7] Mitsias, P. D., Jacobs, M. A., Hammoud R., et al.: Multiparametric MRI ISODATA ischemic lesion analysis: correlation with the clinical neurological deficit and single-parameter MRI techniques. Stroke 33, 2839–2844 (2002).

[8] Bagher-Ebadian, H., Jafari-Khouzani, K., Mitsias, P. D., et al.: Predicting final extent of ischemic infarction using artificial neural network analysis of multiparametric MRI in patients with stroke. PloS one 6(8), e22626 (2011).

[9] Vilela, P., Rowley, H. A.: Brain ischemia: CT and MRI techniques in acute ischemic stroke. Eur J Radiol 96, 162–172 (2017).

[10] Peisker, T., Koznar, B., Stetkarova, I., et al.: Acute stroke therapy: a review. Trends Cardiovasc Med 27, 59–66 (2017).

[11] Parsons, M. W.: Perfusion CT: is it clinically useful?. Int J Stroke 3, 41–50 (2008).

[12] Furlanis, G., Ajčević, M., Stragapede, L., et al.: 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, 2200–2207 (2018).

[13] Granato, A., D'Acunto, L., Ajčević, M., et al.: A novel computed tomography perfusion-based quantitative tool for evaluation of perfusional abnormalities in migrainous aura stroke mimic. Neurol Sci 41, 3321–3328 (2020).

[14] Ajčević, M., Furlanis, G., Miladinović, A., et al.: Early EEG Alterations Correlate with CTP Hypoperfused Volumes and Neurological Deficit: A Wireless EEG Study in Hyper-Acute Ischemic Stroke. Ann Biomed Eng (2021). doi: 10.1007/s10439-021-02735-w.

[15] Ajčević, M., Furlanis, G., Stella, A. B., et al.: A CT perfusion based model predicts outcome in wake-up stroke patients treated with recombinant tissue plasminogen activator. Physiol Meas 41(7), 075011 (2020). doi: 10.1088/1361-6579/ab9c70.

[16] Campbell, B. C., Weir, L., Desmond, P. M., et al.: CT perfusion improves diagnostic accuracy and confidence in acute ischaemic stroke. J Neurol Neurosurg Psychiatry 84(6), 613–8 (2016) .

[17] Adams Jr., H.P., Davis, P.H., Leira, E.C., et al.: Baseline NIH stroke scale score strong-ly predicts outcome after stroke: a report of the trial of org 10172 in acute stroke treat-ment (TOAST). Neurology 53, 126–131 (1999).

[18] Wilson, J. L., Hareendran, A., Grant, M., et al.: Improving the Assessment of Outcomes in Stroke: Use of a Structured Interview to Assign Grades on the Modified Rankin Scale. Stroke 33(9), 2243–2246 (2002).

[19] Barber, P. A., Demchuk, A. M., Zhang, J., et al.: The validity and reliability of a novel quantitative CT score in predicting outcome in hyperacute stroke prior to thrombolytic therapy. Lancet 355, 1670–1674 (2000).

[20] Wintermark, M., Flanders, A. E., Velthuis, B., et al.: Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. Stroke 37, 979–985 (2006).

[21] Tibshirani, R.: Regression shrinkage and selection via the Lasso. J R Stat Soc 58, 267–288 (1994).

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

[23] Ajčević, M., Furlanis, G., Naccarato, M., et al.: Hyper-acute EEG alterations predict functional and morphological outcomes in thrombolysis-treated ischemic stroke: a wireless EEG study. Med Biol Eng Comput 59(1),121-129 (2021). doi: 10.1007/s11517-020-02280-z.

[24] Agarwal, S., Jones, P. S., Alawneh, J. A., et al.: Does perfusion computed tomography facilitate clinical decision making for thrombolysis in unselected acute patients with suspected ischaemic stroke?. Cerebrovasc Dis 32, 227–233 (2011).

[25] Campbell, B. C. V., Ma, H., Ringleb, P. A., et al.: 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 394(10193), 139–147 (2019).

[26] Shankar, J. J. S., Langlands, G., Doucette, S., et al.: CT Perfusion in Acute Stroke Predicts Final Infarct Volume- Inter-observer Study. Can J Neurol Sci 43, 93–97 (2016).

[27] Padroni, M., Bernardoni, A., Tamborino, C., et al.: 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 (2016).

[28] Lin, K., Do, K. G., Ong, P., et al.: Perfusion CT improves diagnostic accuracy for hyper-acute ischemic stroke in the 3-hour window: study of 100 patients with diffusion MRI confirmation. Cerebrovasc Dis 28, 72–79 (2009).