A Radiomics-based Machine Learning Approach to Assess Collateral Circulation in Ischemic Stroke on Non-contrast Computed Tomography

Mumu Aktar[1][0000−0002−5718−7238], Yiming Xiao[1][0000−0002−0962−3525], Donatella Tampieri[2], Hassan Rivaz[3][0000−0001−5800−3034], and Marta Kersten-Oertel[1][0000−0002−9492−8402]

[1] Department of Computer Science and Software Engineering, Concordia University, 1455 boul. De Maisonneuve O., Montreal, Québec, H3G 1M8, Canada.
m_ktar@encs.concordia.ca

[2] Department of Diagnostic Radiology, Kingston Health Sciences Centre, Kingston General Hospital, Kingston, Ontario, K7L 2V7, Canada.

[3] Department of Electrical and Computer Engineering, Concordia University, 1455 boul. De Maisonneuve O., Montreal, Québec, H3G 1M8, Canada.

Abstract. Assessment of collateral circulation in ischemic stroke, which can identify patients for the most appropriate treatment strategies, is currently conducted with visual inspection by a radiologist. Yet numerous studies have shown that visual inspection suffers from inter and intra-rater variability. We present an automatic evaluation of collaterals using radiomic features and machine learning based on the ASPECTS scoring terminology with non-contrast computed tomography (NCCT). The method includes ASPECTS region identification, extraction of radiomic features, and classification of collateral scores with support vector machines (SVM). Experiments are performed on a dataset of 64 ischemic stroke patients to classify collateral circulation as good, intermediate, or poor and yield an overall area under the curve (AUC) of 0.86 with an average sensitivity of 80.33% and specificity of 79.33%. Thus, we show the feasibility of using automatic evaluation of collateral circulation using NCCT when compared to the ASPECTS score by radiologists using 4D CT angiography as ground truth.

Keywords: Ischemic stroke · Collateral circulation · Computer-aided diagnosis · Non-contrast CT · Machine Learning · Radiomics.

1 Introduction

Acute ischemic stroke (AIS) caused by blocked arteries in the brain is one of the leading causes of death worldwide. Treatment strategies of AIS vary from intravenous tissue plasminogen activator (IV-tPA) to endovascular thrombectomy treatments (EVT) based on the time window and patients' conditions. EVT is one of the best treatments for restoring blood flow through blocked arteries but its success rate depends on the extents of a patient's collateral circulation. Collateral circulation is a secondary vascular network that is recruited temporarily

that allows for the survival of viable brain tissues when the main conduits fail due to ischemic stroke. The extent of leptomeningeal collateral flow from the middle cerebral artery (MCA) flowing to the anterior cerebral artery (ACA) and posterior cerebral artery (PCA) has been shown to be a radiologic surrogate predicting the response of revascularization therapy [12]. However, scoring of the collaterals manually following conventional radiologic strategy suffers from the intra- and inter-rater variability [2], [9, 10], less reliable results, and is time-consuming. Some studies have compared automated approach with visual inspection based on ASPECTS evaluation having greater agreement ($\kappa = 0.90$) than neuroradiologists [18] or slightly worse agreement than human expert ratings [14]. Therefore, developing automatic and robust approaches to collateral evaluation in AIS based on systematic radiologic criteria and methods is important. A number of different approaches have been proposed to score collaterals, for example, ASPECTS (Alberta Stroke Program Early CT Score) [24], the collateral score of the Society of NeuroInterventional Surgery/Society of Interventional Radiology (ASITN/SIR) based on conventional angiography [11] which is adapted to be applicable to dynamic computed tomography angiography (CTA) further in the study of Sekar *et al.* [26], the scores of Christoforidis *et al.* [6], Miteff System [20], Mass System [17], modified Tan Scale [29], regional leptomeningeal collateral score (rLMC) [19], collateral evaluation with 4D-CTA based on ASPECTS [15], [31], and ACCESS [2].

ASPECTS is one of the most reliable, systematic and robust approaches shown to have positive clinical outcomes in ischemic damage detection in many studies (e.g. [7,16,25–28]) with baseline CTA source images(CTA-SI), CT perfusion images(CTP), contrast-enhanced CT (CECT), non-contrast CT (NCCT), and timing invariant CTA (TiCTA) modalities respectively. Although some studies [3, 5, 25] show that contrast-enhanced CT has superior performance delineating brain vasculature, these are limited to manual intervention or semi-quantitative approaches. Different studies (Brainomix: e-ASPECTS, e-CTA, iSchemaView: Rapid CTA, Rapid ASPECTS, Syngo.via Frontier ASPECT Score Prototype V2: not clinically approved) have focused on automating ASPECTS using artificial intelligence and feature-based machine learning. The e-ASPECTS software from Brainomix Ltd. (Oxford, UK) and RAPID ASPECTS by iSchemaView (Menlo Park, USA) are the only two certified clinical software for ischemic damage detection using ASPECTS on NCCT. Although they are not intended yet to be used as stand-alone diagnostic tools, both suggested NCCT as an alternative to CTP for ischemic damage quantification [21]. The ability of NCCT to work as the stand-alone diagnostic tool extracting much clinical information was shown by Sheih *et al.* [27]. In their work, the authors compared diffuse hypoattenuation and focal hypoattenuation on contralateral hemispheres in 10-ASPECTS regions and obtained an area under the curve (AUC) of 90.2% for a total of 103 subjects. The study by Kuang *et al.* [16] also performed contralateral analysis using a machine learning-based approach to assess early ischemic changes by classifying the 10-ASPECTS regions based on the differences of contralateral texture features. Taking diffusion-weighted imaging (DWI) as ground truth, this

study with 257 patients obtained an AUC of 0.89 between the proposed method and experts' reading. Our work resembles Kuang *et al.* [16] in that it uses contralateral radiomic features, however unlike their work we evaluate collateral circulation rather than early ischemic damage.

Since NCCT is easily available and used as a front-line diagnostic tool in clinical settings, also being free from contrast agent that can cause adverse effects to some patients, we used NCCT to automatically assess scoring in acute ischemic stroke based on the ASPECTS terminology. Unlike most of the state-of-the-art methods of automating ASPECTS to obtain ischemic damage by assessing hypoattenuation using DTI as ground truth, we used 4D CTA as ground truth to evaluate collaterals scored through observing multiple phases by radiologists. We aim to evaluate collaterals using NCCT with radiomic feature extraction in the MCA territory of left/right hemispheres and classify them into good, intermediate, or poor categories with support vector machines (SVM). Since brain collaterals vary between individuals and represent symmetric characteristics between left/right hemispheres of the same individual, we extracted radiomic features from each side of the hemispheres of a subject separately and took the difference between them to obtain the non-symmetry. Fig. 1 shows the different collateral categories in contrast-enhanced CTA. To the best of our knowledge, this is the first study using NCCT to evaluate the collateral circulation. The underlying assumption of our novel approach is that we can identify regions with insufficient collateral circulation using radiomic features based on tissue degeneration which may be captured on NCCT and score the extent of collaterals using these features.

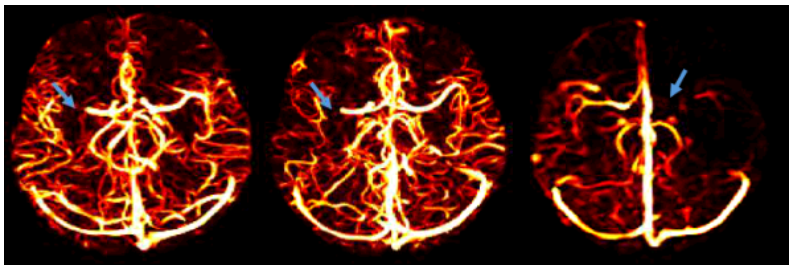

Fig. 1. From left to right, an example of good, intermediate and poor collaterals on contrast-enhanced CTA. The blue arrow indicates the occlusion on the MCA.

2 Materials and Methods

2.1 Scanning Protocols

We have evaluated our method with 8 poor, 17 intermediate, and 39 patients with good collaterals. All 64 subjects underwent imaging at the Montreal Neurological Hospital (Montreal, Canada). A Toshiba Aquilion ONE 320-row detector

640-slice cone-beam CT (Toshiba medical systems, Tokyo, Japan) scanner, which provides whole-brain perfusion and dynamic vasculature information in one single examination with a single rotation of the gantry, was used to capture the 4D CTA. A series of intermittent volume scans are performed for 60 seconds with a scanning speed of 0.75 s/rotation to capture a total of 19 volumes for each patient with low-dose scanning for every 2s during the arterial phase and 5s during the venous phase. The 19 volumes are divided into 5 groups according to the tube current. The first volume, which we use in our method, is captured before contrast arrival. Isovue-370 (Iopamidol) was used as the non-ionic and low osmolar contrast medium to visualize the vessels in the remaining volumes.

2.2 Ground Truth Labels

The ground truth for collateral circulation was based on scoring by two radiologists examining the 4D CTA images. Following the ASPECTS scoring terminology, the radiologists' defined patients with 0-50% collaterals as poor, greater than 50% and less than 100% as intermediate and 100% collaterals as good.

2.3 Mapping of ASPECTS Regions

Prior to the collateral evaluation, we employed atlas registration to align the 10-ASPECTS regions in all patients. The atlas is generated by extracting the ASPECTS regions from the MNI structural atlas and Harvard Oxford atlas using FSL. Following the ASPECTS score in acute stroke [1] and the study of Pexman *et al.* [24], we extracted the insular ribbon (I), caudate (C), Lentiform nucleus (L), internal capsule (IC), M1 (anterior to the anterior end of the Sylvian fissure including frontal operculum), M2(anterior temporal lobe), M3(posterior temporal lobe), M4 (Anterior MCA territory), M5 (Lateral MCA territory) and M6 (Posterior MCA territory). These are rostral to basal ganglia and approximately 2cm superior to M1, M2 and M3 respectively.

Three steps were performed to map the atlas to the subject brain. First, as the atlas we extracted is in MNI template space, it was mapped onto an average CT template (created using 12 healthy subjects' brains following the unbiased group-wise registration approach by Fonov *et al.* [8]) using affine registration. Next, the CT template was registered to the subjects' native space using symmetric normalization (SyN). Finally, the transformations obtained from the previous steps were used to map the atlas to each subject to delineate specific ASPECTS regions in all subjects. All registration steps were done using Advanced Normalization Tools (ANTs) (stnava.github.io/ANTs). We extracted the brain from each subject using FSL following the study of Muschelli *et al.* [22]. Fig. 2 shows the ASPECTS regions mapped onto a subject.

2.4 Pre-processing

The skull was removed from the NCCT images following the study of Muschelli *et al.* [22]. In this work each image is thresholded within the brain tissue range

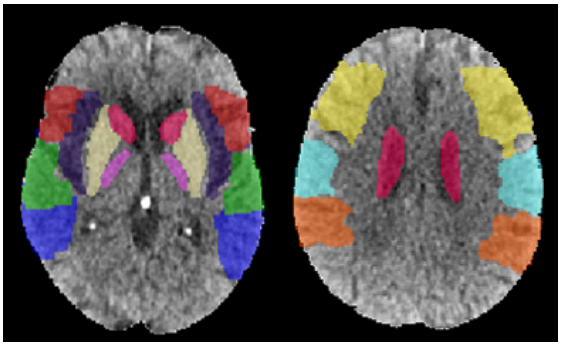

Fig. 2. The 10-ASPECTS regions mapped to an individual patient's brain

of 0-100 Hounsfield units (HU) before skull stripping thus removing any calcifications with very high-intensity values, which were present in some of our patients. Further, a Gaussian pyramid from the multi-scale image representation approach using the kernel from the study of Burt *et al.* [4] was applied to perform smoothing and sub-sampling by one level to all subjects.

2.5 Image Features

The study of Shieh *et al.* [27] shows that ischemic damage can be identified through focal and diffuse hyper attenuation occurring in any ASPECTS region. Following the study of Shieh *et al.*, a deviation and a contrast map were extracted from each side of the brain in order to highlight the areas with insufficient collaterals due to ischemic damage. The deviation and contrast degradation in the areas with less collaterals can be obtained comparing the difference between affected and unaffected sides of the brain. Therefore, the deviation map, D_{map} is generated from each side of brain by subtracting each voxel's intensity, $V(x, y, z)$ from the mean voxel intensity, V_μ and normalizing it with the standard deviation, V_σ using the equation 1.

$$D_{map} = \frac{V(x, y, z) - V_\mu}{V_\sigma} \tag{1}$$

On the other hand, a contrast map is obtained from each side choosing the edges with maximum gradient using the Sobel operator. Rather than comparing the deviation and contrast map between both sides using threshold as the study of Shieh [27], radiomic features are extracted automatically from the maps separately to obtain the spatial relation of voxels and finally the difference between features from each hemisphere is taken (Fig. 3 shows the feature maps with the radiomic features). The feature classes used include radiomic features for the 3D subjects from the study of Van *et al.* [30], as described below.

Gray Level Co-occurrence Matrix (GLCM): The co-occurrence of voxels for specific values are used to examine the textures of the images by statistical

measurement of energy, contrast, entropy, homogeneity, correlation, variance, sum average, autocorrelation, and dissimilarity.

Gray Level Size Zone Matrix (GLSZM): The gray level zone of each subject is quantified by computing the number of voxels that share the same gray level intensity in a 26-connected region.

Global Features: Along with GLCM and GLSZM, the global features of mean, energy, entropy, variance, skewness, and kurtosis of the entire MCA territory from both sides were considered.

In total, 56 features are extracted from the deviation and contrast maps from each side of the brain.

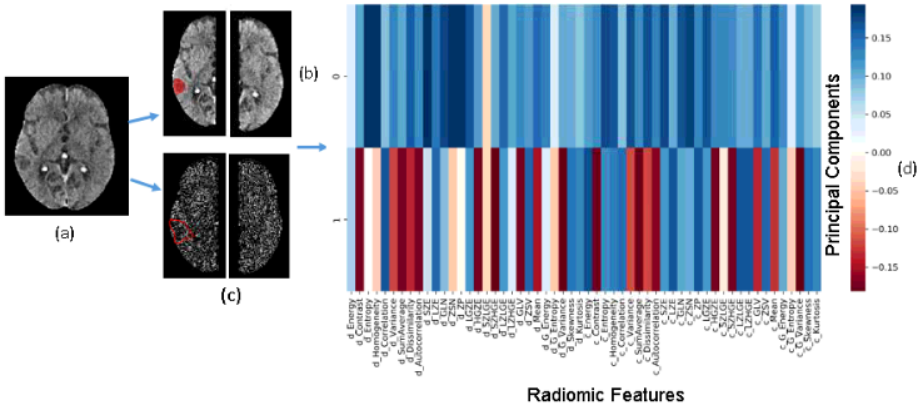

Fig. 3. Feature maps with occlusion and radiomic features (a) Original brain image (b) Deviation maps of left and right hemispheres with highlighted occlusion (c) Contrast maps of both sides with the degradation shown in a polygon (d) Radiomic features

2.6 Classification of Collaterals

Before feeding the radiomic features obtained from the difference of the hemispheres into a classifier, they were ranked using Principal Component Analysis (PCA) with 97% variance. Fig. 3(d) shows the radiomic features' correlation with the first two principal components where the color bar represents the weight of correlation. For example, the GLCM features: *d_Energy*, *d_Homogeneity* from the first principal component have the highest correlation of 0.19 with the principal component which is also visible from the color bar range. The feature names are distinguished starting with 'd' for deviation map and 'c' for contrast map. These are then fed into the One-Vs-Rest SVM classifier with the radial basis function (RBF) kernel using balanced class weight (to penalize the majority class) to classify collaterals into good, intermediate, or poor cases.

3 Results

We applied k-fold (k=10) cross-validation and the performance of the developed method was evaluated using receiver operating characteristic (ROC). We obtained an overall area under the curve (AUC) of 0.86 for best sensitivity and specificity with AUC of 0.85 for poor, 0.90 for intermediate, and 0.83 for good collaterals (Fig. 4). An average sensitivity of 80.33% and specificity of 79.33% were obtained by taking the mean true positive and false positive rates of the three classes. The feature ranking and classification were performed using scikit-learn [23].

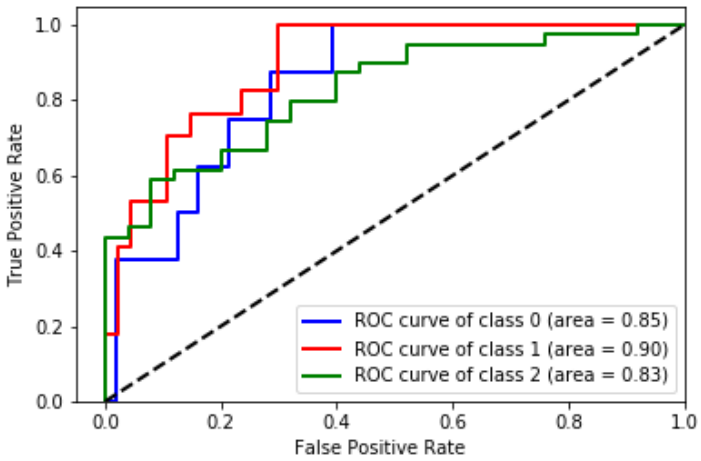

Fig. 4. ROC curve showing classification performance of good, intermediate and poor collaterals.

Further, we compared SVM performance with the Random Forest (RF). However, due to our small sample size and imbalanced dataset, RF performed extensive model selection which led to over-fitting. Thus although we had a high training accuracy (98%), the testing accuracy was 55% in the case of RF.

All the experiments were performed on a Windows 7 machine equipped with an Intel(R) Core(TM) i7-4770 CPU @ 3.40GHz and 28 GB of RAM. The robust and automatic approach grades collaterals quickly (i.e. in approximately 10 minutes with 3 minutes for the registration step, less than 6 minutes for feature extraction and 1 minute to classify a single patient).

4 Discussion

In the current study, we developed an automatic approach for collateral grading based on ASPECTS terminology using NCCT. This is a novel modality for assessing collaterals which are an independent predictor of good clinical outcomes.

Most of the studies use dynamic CTA to assess the collateral grading whereas we proposed classifying collaterals based on ischemic damage from NCCT which requires less time, no bolus, and less radiation. To analyze the relationship between ischemic damage and collateral status, the agreement between e-CTA, which assesses collaterals with machine learning using CTA-CS [29] and e-ASPECTS from e-STROKE SUITE (Brainomix Ltd.,) is shown in the study of Grunwald *et al.* [10]. Our method uses 4D CTA as ground truth to obtain the collateral status from multiple phases and assesses it automatically from single-phase NCCT which resembles radiologists' scores and methodology.

The proposed method automatically scores collaterals using SVM based classifier which is a popular classification method used in many other ischemic stroke analysis studies and more insights can be found in the study of Kamal *et al.* [13]. Since each subject's bilateral sides resemble each other, the collateral extent can be identified from the non-symmetry of both sides. Following this idea, the difference of radiomic features between each side helps to identify ischemic damages automatically without manual intervention indicating insufficient collateral regions in the MCA territory. The atlas-based ASPECTS regions mapping to individual patients helps to improve the performance of the classifier and validate our method based on the popular ASPECTS scoring terminology.

A limitation of this study is the small dataset which is the main challenge of training a classifier. To have a reasonable ratio of train test data, we used 10-fold cross-validation. Since we have only 8 poor cases, this splitting doesn't confirm a poor case to test in each fold. In future work, we will validate our method's performance with more data before applying it to clinical trials.

In conclusion, we have implemented a machine learning-based collateral grading method using NCCT that may replace high-contrast and radiation-based CTA. By using 4D CTA based collateral scoring as ground truth, this novel approach can evaluate collaterals from the tissue degeneration extracted by radiomic features in NCCT. Our results show the feasibility of using NCCT to help physicians identify suitable patients for revascularization in AIS.

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