Deep Learning for Prediction of Mechanism in Acute Ischemic Stroke Using Brain MRI

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Deep learning for prediction of mechanism in acute ischemic stroke using brain MRI

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ABSTRACT

Acute ischemic stroke is a disease with multiple etiologies. Classifying the mechanism of acute ischemic stroke is therefore fundamental for treatment and secondary prevention. The TOAST classification is currently the most widely-used system, but it has limitations of often classifying unknown causes and inadequate inter-rater reliability. Therefore, we tried to develop a 3D-convolutional neural network(CNN) based algorithm for stroke lesion segmentation and subtype classification using only diffusion and adc information of acute ischemic stroke patients. The recruited patients were 2251 patients with acute ischemic stroke who visited Chungbuk National University Hospital from February 2013 – July 2019. Our segmentation model for lesion segmentation in the training set achieved a Dice score of 0.843±0.009. The subtype classification model achieved an average accuracy of 81.9%, and each subtype was Large artery astherosclerosis (LAA) = 81.6%, Cardioembolism (CE) = 86.8%, Small vessel occlusion (SVO) = 72.9%, and Control = 86.3%. In conclusion, the proposed method shows great potential for identification of diffusion lesion segmentation and stroke subtype classification. As deep learning systems gradually develop, it would be useful in clinical practice and application.

Introduction

Acute ischemic stroke has various causes based on the causative mechanism, and it consists of large artery astherosclerosis, cardioembolism, small vessel disease, stroke of other determined etiology, or stroke of undetermined etiology. The classification of acute ischemic strokes based on cause is important for their treatment and secondary prevention. The most widely used classification system is the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification[1,2]. However, this classification method showed moderate inter-rater reliability in classifying acute ischemic stroke and had the limitation of often classifying strokes to be of undetermined etiology[3]. To overcome this limitation, efforts are underway to develop a computerized algorithm for acute stroke diagnosis, but it has not shown sufficient results[4,5].

Various diagnostic methods, such as brain imaging and heart tests, are needed to determine the causative mechanism of acute ischemic stroke. Diagnosing the stroke subtype early through this classification system can positively affect the patients' treatment, prognosis, and secondary prevention[1]. Diffusion weighted MR imaging is a widely used modality for acute stroke diagnosis. It has superior performance in detecting hyperacute lesions and very small ischemic lesions, and in distinguishing chronic and acute lesions[6] compared to brain CT and conventional MRI. Furthermore, when the apparent diffusion coefficient (ADC) map and diffusion weighted image (DWI) are used simultaneously, it is known that the lesion of acute ischemic stroke can be more accurately distinguished and important information is given to the time window of the lesion[7]. The diffusion imaging lesion pattern, which provides useful information for early diagnosis of acute ischemic stroke, has been reported to be closely related to the stroke subtype[8,9].

To diagnose acute ischemic stroke in brain MRI images, various deep learning algorithms based on convolutional neural networks (CNNs) have been proposed[10–21]. These studies have shown that deep learning can detect stroke lesions more accurately than traditional machine learning techniques and can extract meaningful features for severity evaluation or prognosis prediction. Some researchers proposed lesion segmentation techniques for acute ischemic stroke patients based on a U-Net architecture[16,17]. To efficiently exploit the contextual information of volumetric MRI data, Zhang et al.[18] proposed a stroke lesion segmentation technique using a 3-D fully connected-DenseNet. Although the aforementioned studies demonstrated

that deep learning can classify acute ischemic stroke patients via lesion segmentation, a classification technique to predict the treatment mechanism of acute ischemic stroke is yet to be reported. In this paper, we present a 3D CNN-based models for stroke lesion segmentation and subtype classification using only DWI and ADC images of acute ischemic stroke patients.

Results

Lesion segmentation model

Our segmentation model for lesion segmentation in the training set achieved a Dice score of 0.891±0.034. For the test set, our model resulted in a Dice score, precision, and recall of 0.843±0.009, 0.842±0.012, and 0.844±0.017, respectively. Figure 1 demonstrates some examples of lesion prediction results compared with assessment by neurologist raters. Our segmentation model accurately predicted even extremely small lesions. Meanwhile, most failure cases have occurred when the lesions have very poor contrast in diffusion images, as demonstrated in Figure 2.

Stroke subtype classification model

The average accuracy of subtype classification was 81.9%. The accuracy of each subtype was 81.6%, SVO 86.8%, CE 72.9%, and control 81.9%. Figure 3 presents the confusion matrix obtained using the subtype classification model. our model showed lower accuracy on SVO compared with other subtypes, indicating that the model confused SVO with control cases due to its poor analysis performance for small lesions.

Discussion

This is the first study to perform subtype classification of stroke mechanism by analyzing patterns of acute ischemic stroke lesions through deep learning based on 3D-CNN using DWI and ADC in acute ischemic stroke patients. The main findings of this study are as follows. First, the 3D-CNN-based segmentation accuracy for acute ischemic stroke lesions was 0.843 based on the Dice score. Second, in terms of subtyping to classify the cause of acute ischemic stroke, the predicted degree of cause classification according to the TOAST classification, which is the 'ground truth', was confirmed to be 81.3% for LAA, 84.6% for SVO, and 73.0% for CE, respectively.

Brain imaging plays a crucial role in diagnosing and identifying mechanisms for developing acute ischemic stroke according to technological advances[22]. Among the various MR sequences, DWI and ADC map are useful tools for early detection of acute ischemic lesions and differentiating between stroke mimics and acute ischemic stroke[23]. Several previous studies have attempted to segment the infarction volume of acute ischemic strokes in MRI using artificial intelligence. Various imaging patterns of acute ischemic stroke in DWI lesion are known to be correlated with pathogenic mechanisms. In the case of cardiac embolic stroke, acute stroke lesions in DWI often show single cortical/subcortical lesions or occur multiple times in various vascular branches; multiple unilateral lesions in the anterior circulation are characteristic findings of arteriogenic embolism. Meanwhile, one small infarction (2–20mm in diameter) lesion observed in deep acute ischemic stroke white matter, basal ganglia, thalamus, and pons is highly associated with small vessel occlusion[8,24]. We tried to apply the doctor's diagnosis process for determining the cause of acute ischemic stroke based on the characteristic findings in brain MRI using artificial intelligence.

However, there are many limitations in predicting the pathogenesis of acute ischemic stroke using only the DWI/ADC map. The TOAST classification is the most widely used system for classifying acute ischemic stroke according to pathogenesis. Clinical findings and the results of ancillary diagnostic studies, including brain imaging and cardiac evaluation, are used to classify the patients' acute ischemic stroke mechanism[1]. However, despite its ease of use and widespread popularity, the overall inter-rater agreement is moderate, and it is known to be less reliable in small vessel occlusion and strokes of undetermined causes, especially compared to large artery atherosclerosis and cardioembolism[3]. To overcome this, an improved classification method that applies a new diagnostic technique was used, but it still showed limitations[4,5,25,26]. In particular, acute ischemic stroke with unknown mechanisms other than the mechanisms that can be explained, such as large artery atherosclerosis, cardioembolism, small vessel occlusion and stroke of other determined etiology, is called a cryptogenic stroke. It is observed in approximately of patients with ischemic acute ischemic stroke[27]. These cryptogenic strokes are often observed as embolic strokes, and are called embolic strokes of undetermined source (ESUS)[28]. There is a need to find out the mechanism of ESUS and provide proper treatment, but there is no clear method to do so yet[29]. We conducted this study expecting acute ischemic stroke diagnosis through deep learning algorithm to be the answer. We expect our model to be applied to ESUS patients as a useful tool to distinguish cardioembolic stroke and non-cardioembolic stroke.

In addition, this study shows clear differences from previous studies in terms of the improved technology. Since most lesion segmentation techniques are used as single slide input, information from adjacent slides cannot be used; this results in low accuracy[30]. proposed a lesion segmentation technique based on 3D CNN, but its analysis performance was limited due to a relatively shallow network architecture. In contrast, the lesion segmentation technique proposed in our study applied a residual

network to allow stable model learning even in a deep network architecture, and it achieved a high Dice score of 0.845 in the test set. In addition, the proposed subtype classification model achieved an average classification accuracy of 81.9% through an attention mechanism using the lesion information predicted in the lesion segmentation model. Unlike existing models, our technique provides not only the subtype of the stroke, but also the area that the model focused on, to make the predictions. The proposed segmentation and classification models can be readily applicable to various medical AI fields that use 3D volumes such as CT and MRI as input information.

In summary, our study was conducted to help the treatment for prognosis and secondary prevention by predicting more accurate developmental mechanisms of acute ischemic stroke patients. Using solely the initial MRI information, we presented a feasible model that predicts the mechanism of occurrence by applying an algorithm based on 3D-CNN through deep learning. The diffusion lesion volume measurement and stroke subtype classification by our proposed method showed deep correlation with that performed by manual segmentation and subtype classification of professional neurologists. This study has significance as the first study to predict the incidence of acute ischemic stroke using only MRI information.

Methods

Study population

This retrospective study was approved by the Institutional Review Board of Chungbuk National University Hospital, and informed consent was waived. The participants were 2,251 patients with acute ischemic stroke who visited Chungbuk National University Hospital from February 2013 to July 2019. Information on acute ischemic stroke was compiled using the registry. All acute ischemic stroke patients were reviewed by at least 3 stroke specialists and classified according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification. There were a total of 1,768 patients with large artery atherosclerosis, cardioembolism, and small vessel occlusion, excluding stroke of other determined etiology or stroke of undetermined etiology, according to TOAST classification. Among them, 1,408 patients had a DWI and ADC (Figure 4). There were 608 patients with large artery atherosclerosis, 441 patients with cardioembolism, and 359 patients with small vessel occlusion. Among the normal patients who visited the hospital during the same period, 400 patients who showed normal findings on the MRI examination at our clinic were included as controls. All patients' gender, age, and National Institutes of Health Stroke Scale Rating (NIHSS) are listed in Table 1.

Imaging acquisition

MRI was performed using various machines including 1.5 T (Achieva, Philips Healthcare) and 3.0 T (Ingenia CX, Philips Healthcare; Achieva, Philips Healthcare) scanners. The parameters of the DWI sequence are as follows: repetition time of 2500–3000 ms, echo time of 80 ms, slice thickness of 3-5 mm, intersection gap of 1 mm, field of view (FOV) of 220 × 220 mm, matrix size of 256 × 256 (approximately 2 mm × 2 mm in-plane resolution), and b-values of 0 and 1000 s/mm^2. Each ADC map was generated automatically the manufacturer's software.

Data annotation

To produce a "ground truth" reference standard for training and evaluating the subtype classification model, each patient was classified into 4 classes (LAA, SVO, CE, and Control) according to the TOAST classification system. Then, lesion areas in each DWI slide were manually annotated by two experienced neurologists (authors of this article KY and BK) using in-house annotation software. Finally, each lesion was cross-validated and labelled with a final decision agreed upon by both raters.

Lesion segmentation model

Our segmentation model based on 3D CNN called V-Net[31] is illustrated in Figure 5. The model consists of an encoder that extracts the feature maps from the local 3D volumes and a decoder that predicts stroke lesions using the feature maps. Since our model has a very deep architecture, we employed a residual block to alleviate the gradient vanishing and exploding problem. The residual block contains (1) a 3D convolutional layer with kernel size 3x3x3 and (2) a residual skip connection and two 3D convolutional layers with kernel size 3x3x3 each following a batch normalization and rectified linear unit (ReLu), respectively. In the network encoder, residual blocks are utilized for feature extraction and max-pooling layers, with a stride of 2 used to reduce the spectral dimensionality. On the other hand, the decoder consists of up-convolutional layers with strides of 2 followed by residual blocks after the feature map concatenation. Skip connections from layers of equal resolution in the encoder provide high-resolution features to the decoder. In the last layer of the decoder, a sigmoid activation layer is connected to calculate a probability map for stroke lesions.

The model was trained over 200 epochs with an Adam optimizer, an initial learning rate of 1e-5, and a batch size set to 8. The model was trained from scratch without using pre-trained weights. We tested various loss functions such as weighted cross-entropy loss, L1 loss, and Dice loss; Dice loss achieved the best performance. Furthermore, to address the data scarcity

problem, data augmentation techniques such as rigid transformation, horizontal/vertical flip, Gaussian noise, and gamma correction were randomly triggered in each training session.

Subtype classification model

As illustrated in Figure 6, our classification model predicts the probabilities of four classes: LAA, SVO, CE, and Control. For the feature extraction, we adopted the residual block in the lesion segmentation model. In addition, to guide the network focus on the lesions, the feature maps are enhanced by using the lesion prediction results provided via the segmentation model. More specifically, the enhanced feature map F_{enh} is obtained by

$$F_{enh} = F \times (1 + h(A)), \tag{1}$$

where F and A are the feature map extracted by each residual block and the lesion segmentation result, respectively. $h(\cdot)$ is a bilinear interpolation to match the spatial resolutions between F and A. This attention mechanism significantly improved the classification performance of the model by guiding the network to focus on the lesion areas to predict the stroke subtype. The model was trained over 400 epochs with an Adam optimizer, an initial learning rate of 1e-5, and a batch size set to 4. We utilized the categorical cross-entropy loss and the model was trained from scratch. We also used the data augmentation technique used to train the classification model.

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Acknowledgements

Correspondence and requests for materials should be addressed to KY and DL.

Author contributions statement

SP, BK, KY and DL designed this study. Image data was collected by KY and BK. SP designed in-house annotation software and built the annotation platform. Data interpretation and annotation were done by KY and BK. SP developed the models for lesion segmentation and subtype classification and conducted the performance evaluation. SP, BK, KY, DL, MH, and JH contributed to the interpretation of the results. SP, BK wrote the manuscript and KY, DL supervised the project. All authors discussed the results and contributed to the final manuscript.

Competing interests

The author declares no competing interests.

Additional information

No additional information

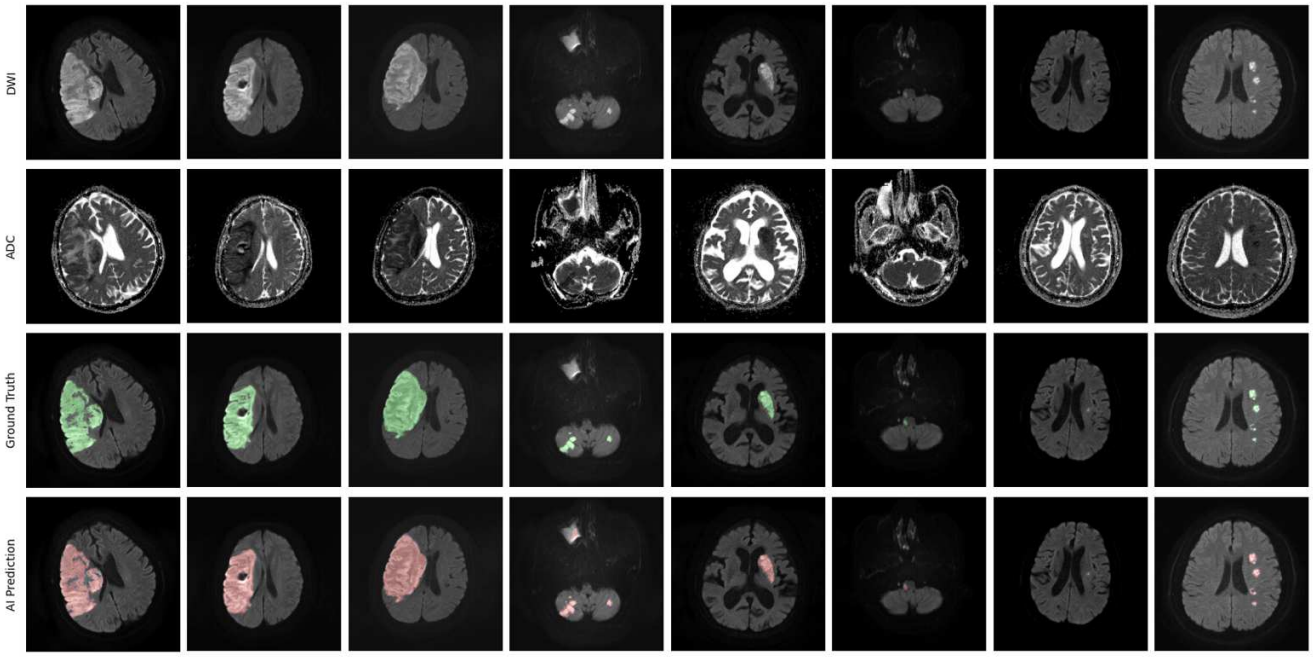


Figure 1. Prediction outcomes using our lesion segmentation model. In each panel, the images in the first and second rows are DWI and ADC slices, respectively. The third ones are the 'ground truth' labels annotated by two neurologists and the fourth ones are lesion areas predicted by our model.

Group		Total	LAA	SVO	CE
N		1,395	600	358	437
Sex	Female	591	250	136	205
	Male	805	351	222	232
Age		69.55±12.19	69.15±11.68	65.52±12.54	73.40±11.42
Delayed time (min)		1495.37±3023.70	1754.84±3908.82	1809.46±2369.00	881.23±1754.88
NIHSS		5.67±5.72	4.96±4.99	3.02±2.13	8.81±7.11

Table 1. Baseline characteristics of the study population according to stroke mechanism. LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism; NIHSS, National Institutes of Health Stroke Scale Rating.

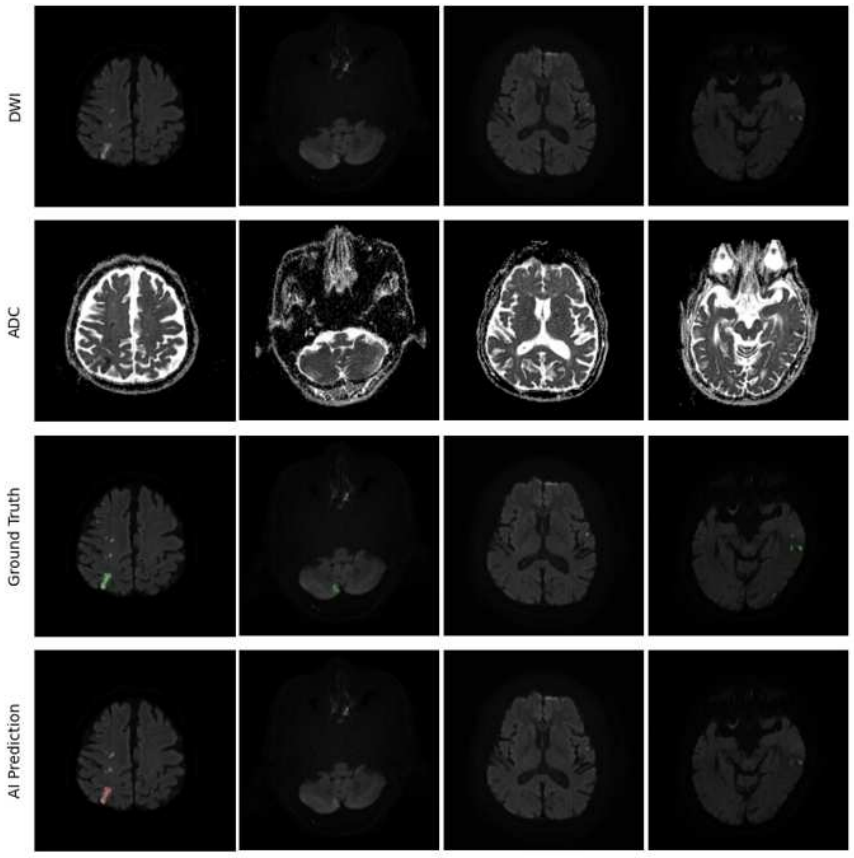


Figure 2. Failure cases of our lesion segmentation model. Most cases have occurred when the lesions have extremely poor contrast.

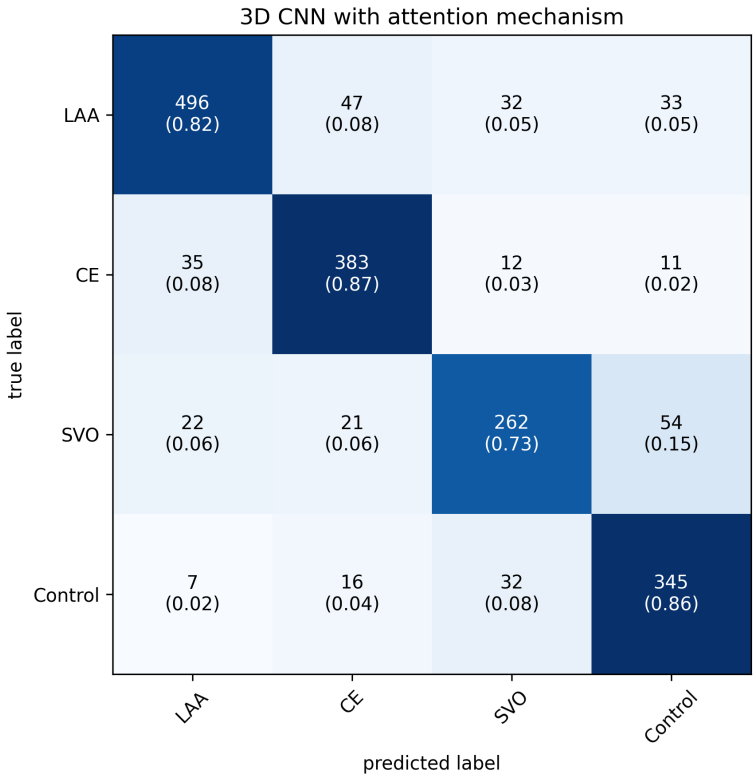


Figure 3. Confusion matrix of our subtype classification model.

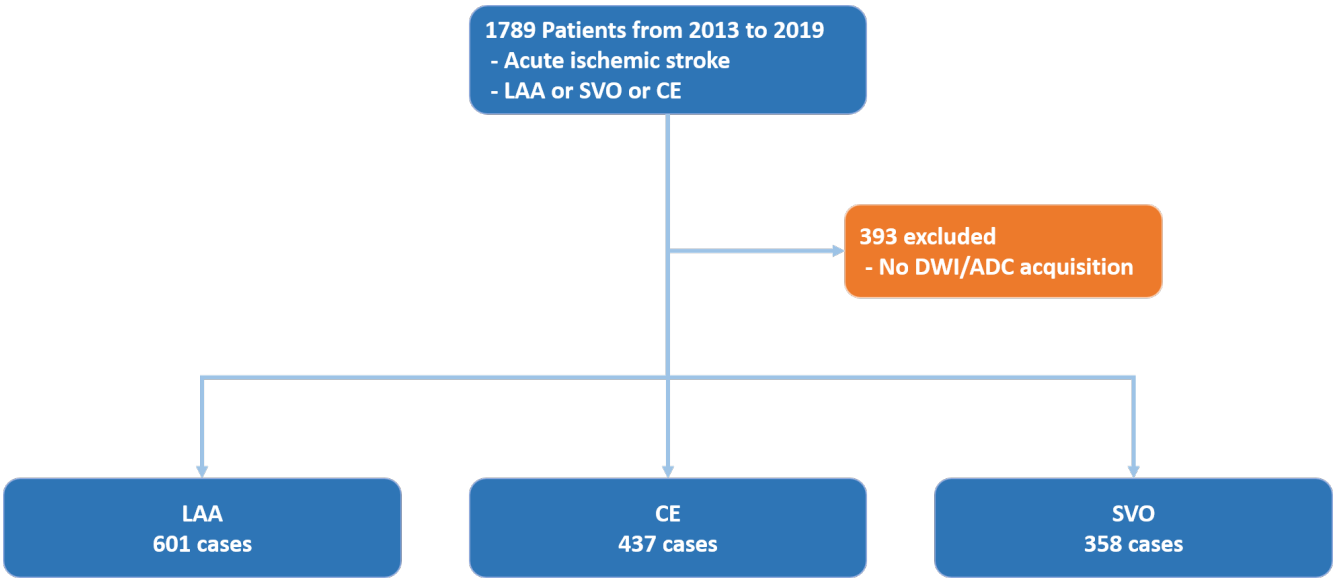


Figure 4. Study profile. LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism; DWI, diffusion weighted image; ADC, apparent diffusion coefficient.

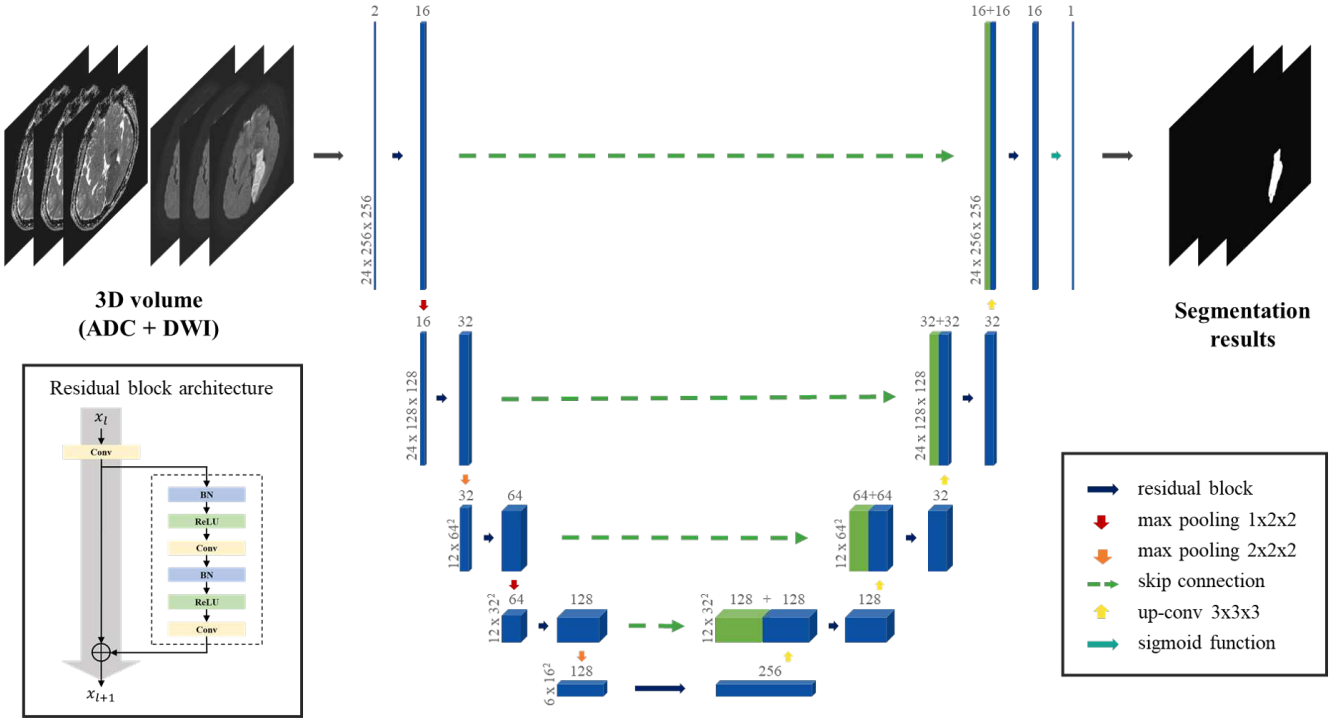


Figure 5. Our network architecture for stroke lesion segmentation. Based on 3D U-Net, the network learns the features based on a hierarchy framework starting from simple features such as edges and shapes and to high-level features in the deeper levels.

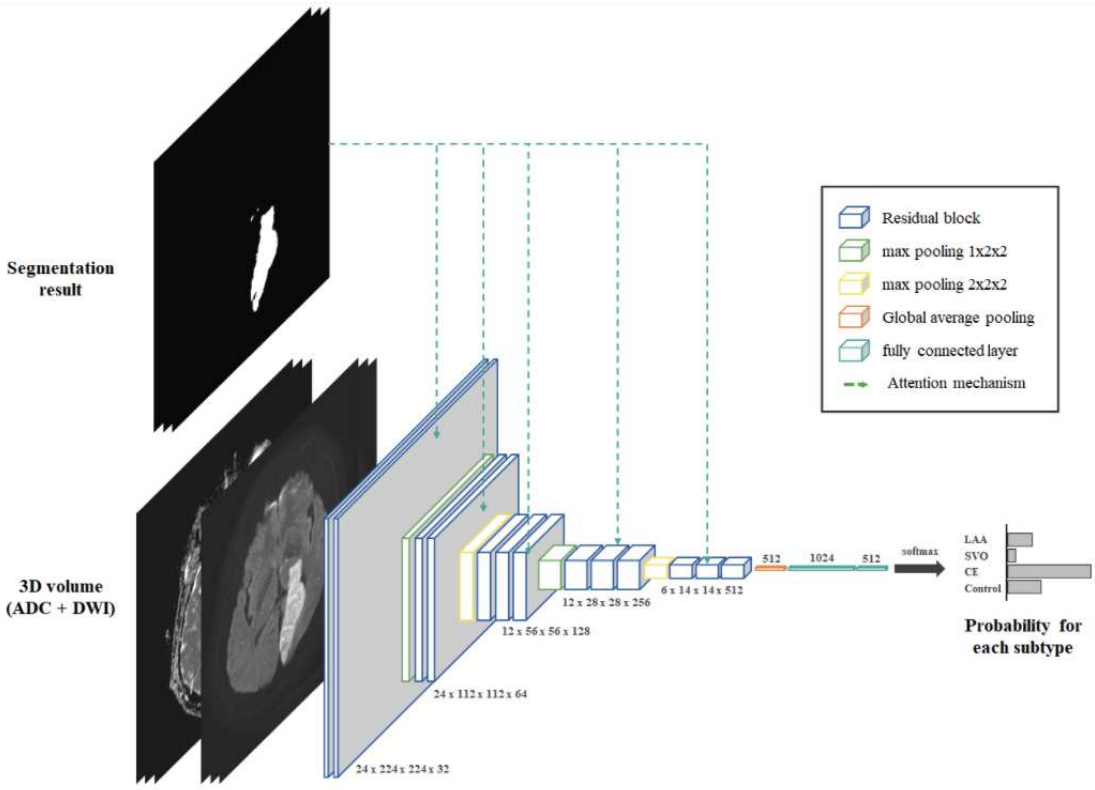
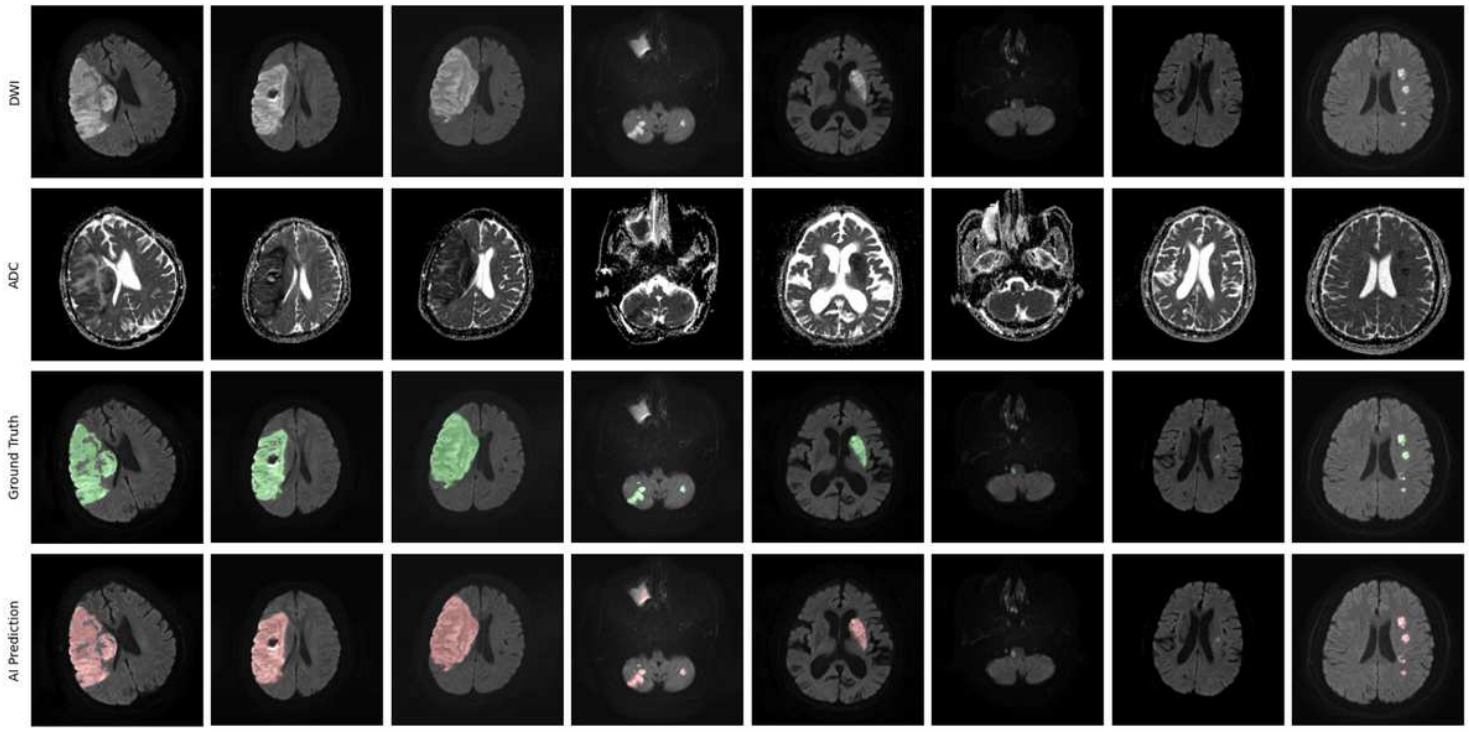


Figure 6. Our network architecture for stroke subtype classification. To guide the network to focus on the lesion areas, we adopted the attention mechanism using the lesion segmentation result.

Figures



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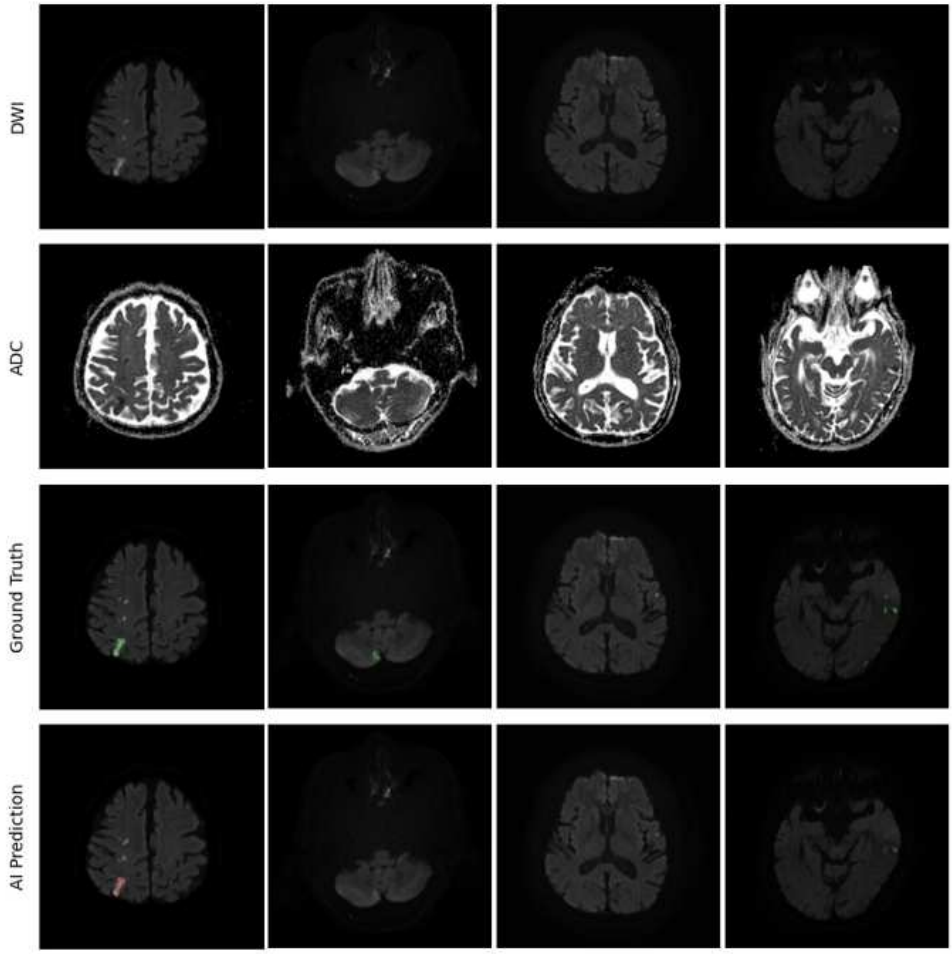

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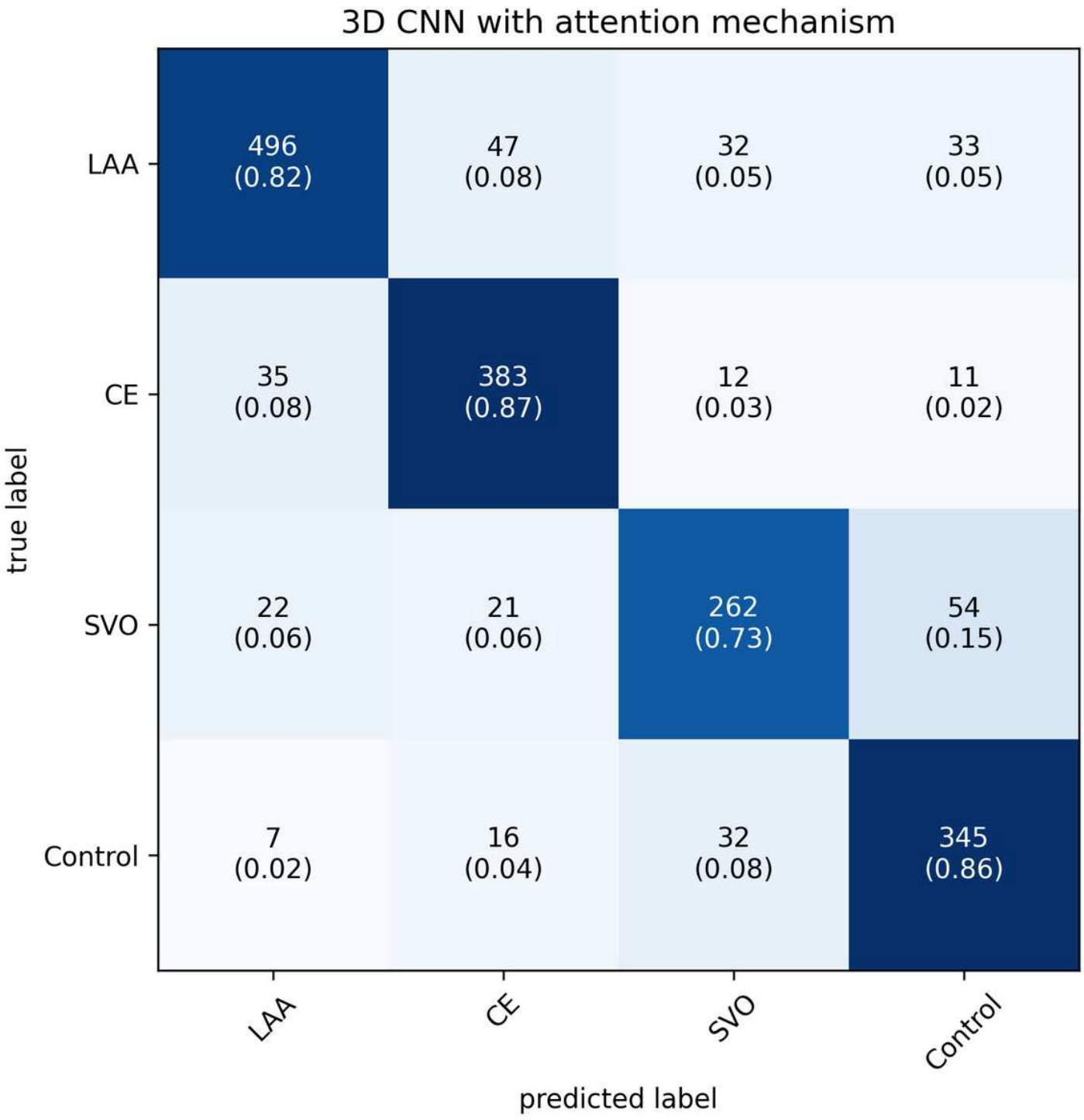


Figure 3

Confusion matrix of our subtype classification model.

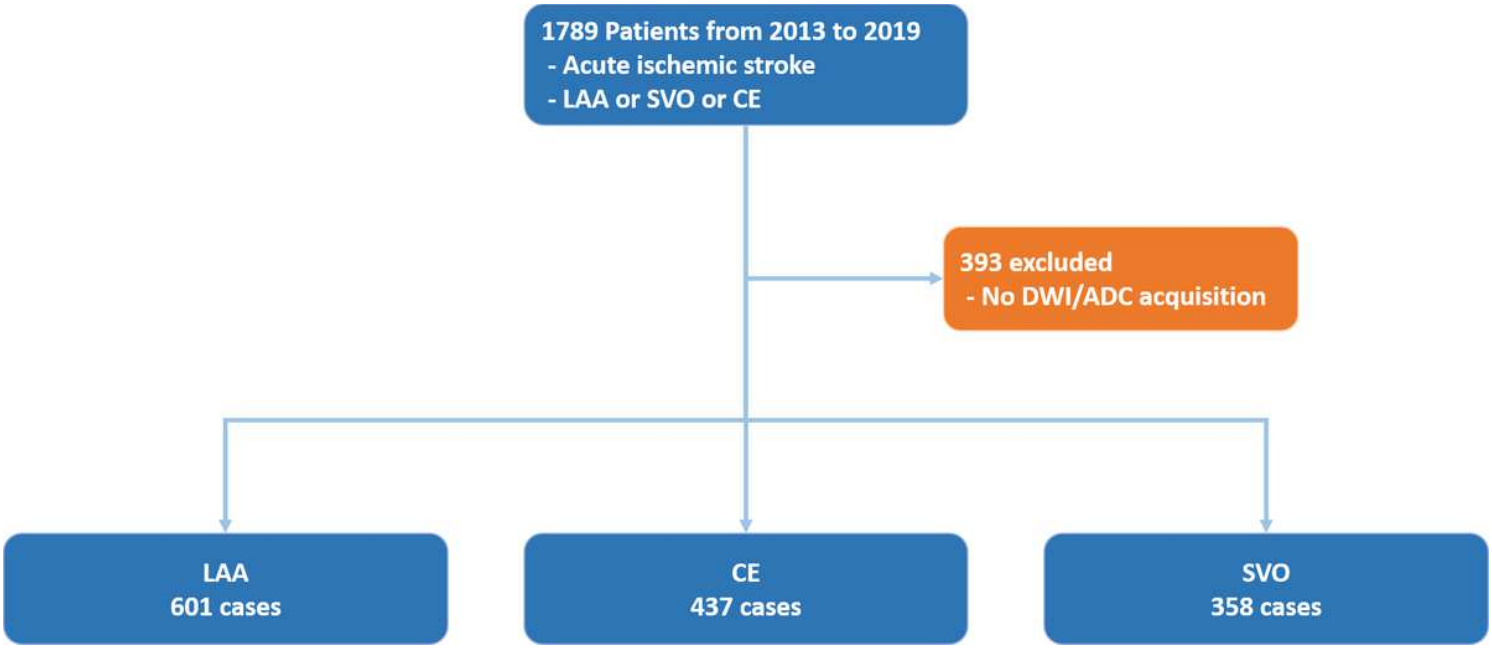
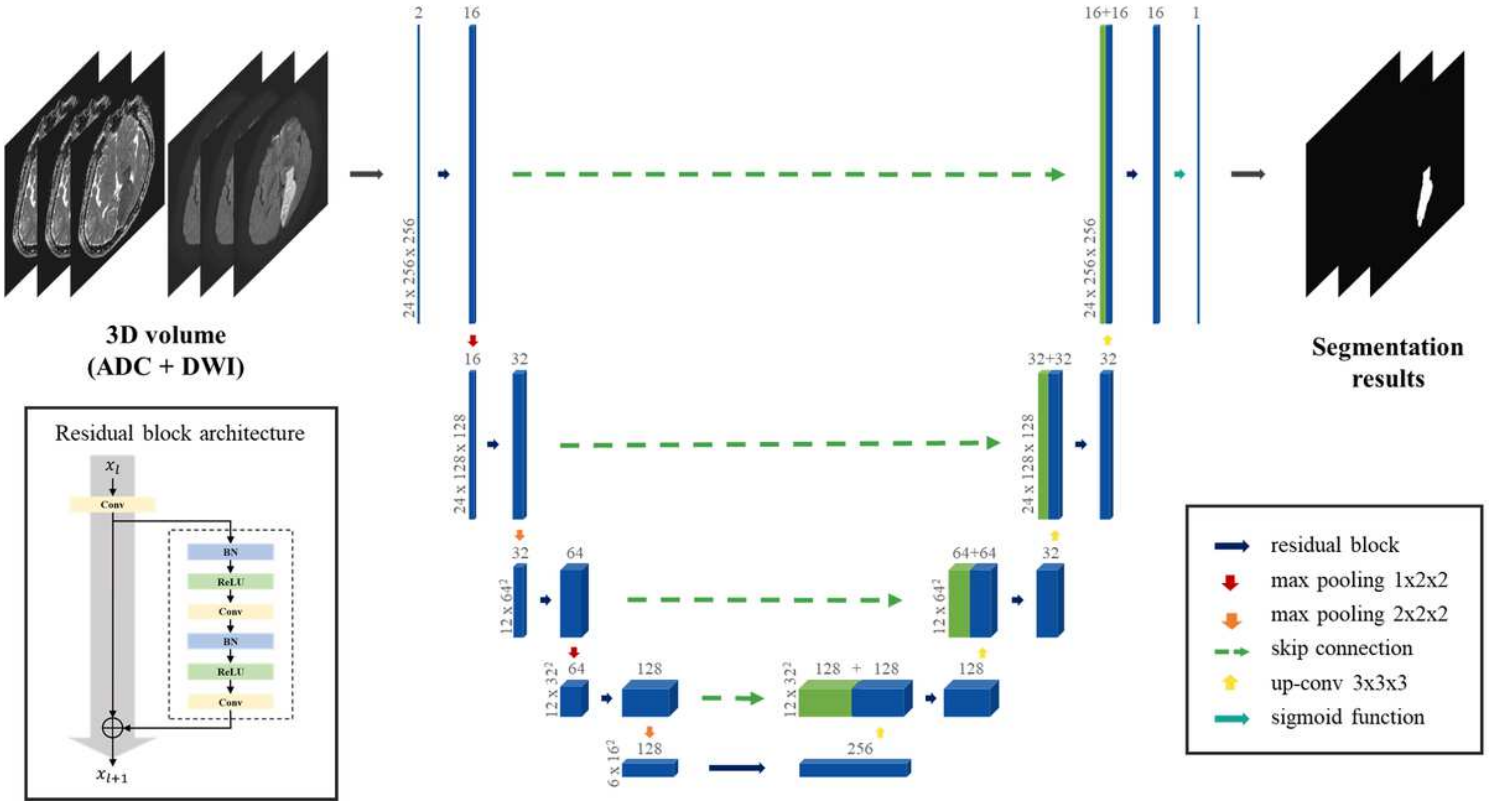


Figure 4

Study profile. LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism; DWI, diffusion weighted image; ADC, apparent diffusion coefficient.



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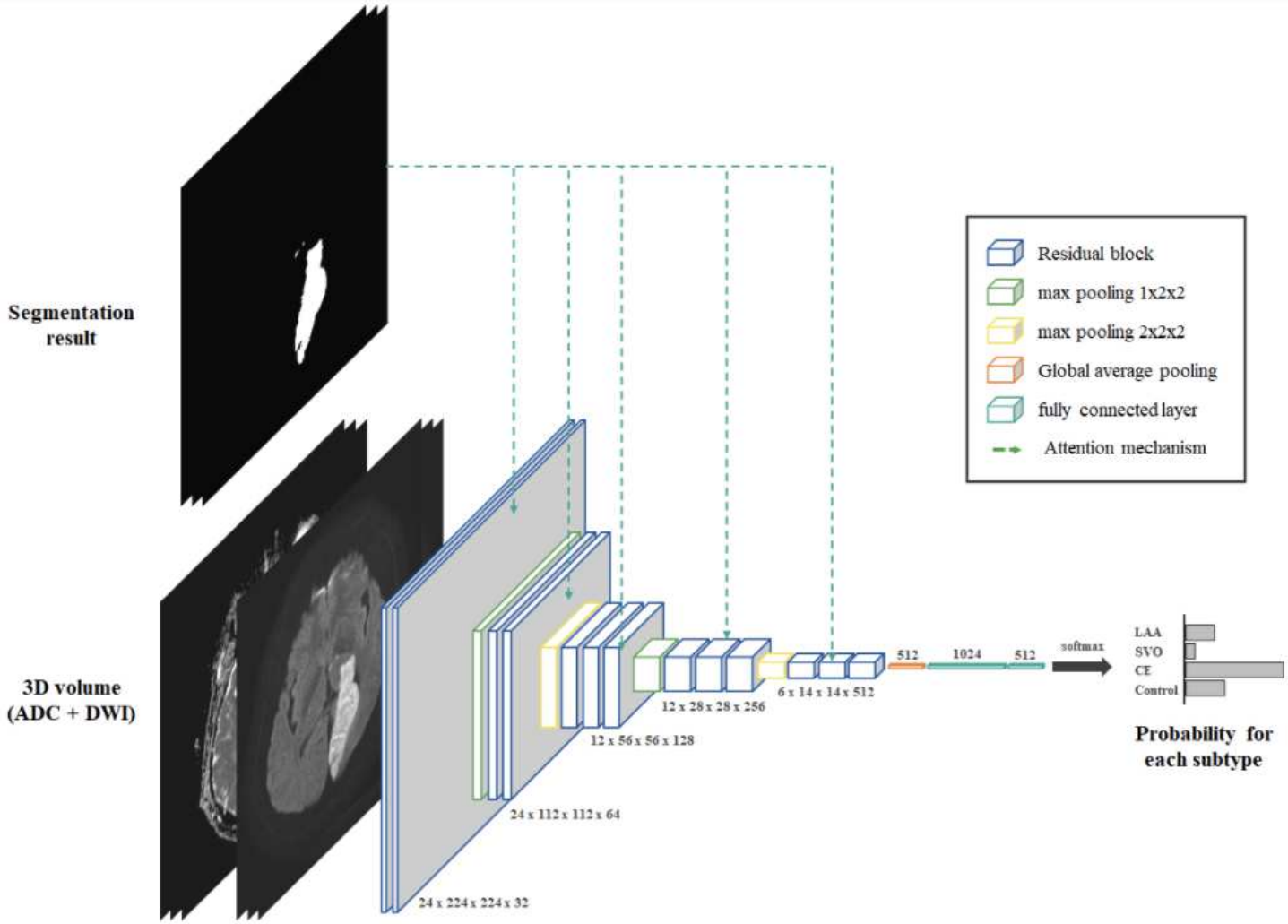

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Our network architecture for stroke subtype classification. To guide the network to focus on the lesion areas, we adopted the attention mechanism using the lesion segmentation result.