Using advanced artificial intelligence imaging software to predict the outcomes of cerebrovascular disease

Stroke is a leading cause of morbidity and mortality worldwide, and a huge amount of national financial budget has been expedited on stroke care from hyperacute to chronic phases of stroke. To lessen the catastrophic impact of stroke on people's life, it is important to prevent the occurrence of stroke by controlling stroke-related risk factors, and once stroke occurs, alleviate the damage caused by stroke.

Stroke can be classified into ischemic and hemorrhagic subtypes, with the former accounting for 70-80% of all strokes.[1]

For the hyperacute treatment of ischemic stroke, besides the well-established safety and efficacy of intravenous tissue-type plasminogen activator (IV-tPA), endovascular thrombectomy (EVT) for patients with a stroke attributable to large vessel occlusion (LVO) is a burgeoning field, following the demonstration of better functional outcomes in patients undergoing EVT compared to those receiving medication alone in a meta-analysis summarizing the results of 5 randomized trials.[2]

The goal of EVT is to achieve recanalization of the occluded arterial segment. However, as every treatment has its downside, the EVT is no exception. Although a substantial portion of stroke patients benefitted from the EVT, some did not get the benefit, and some were even harmed by the EVT due to peri-procedural or post-procedural complications, which includes vessel injury, migration of emboli to different or distal vascular territories, hyperperfusion injury, and hemorrhagic transformation of stroke.[3]Therefore, it is paramount to triage patients most likely to benefit from the EVT.

Following an ischemic stroke, the brain tissues downstream from the occluded artery is deprived of blood supply, which provided the tissue with oxygen and nutrients. Depending on the extent of collateral supply, the brain tissues can still receive adequate perfusion to maintain normal electrophysiologic and homeostatic function (normal), receive sufficient blood supply to maintain basic cellular metabolic needs but unable to function as well as normal tissue (penumbra), or receive little blood supply that is insufficient to maintain even the basic cellular metabolic needs and will die in minutes (ischemic core). The perfusion in the ischemic brain regional is dynamic and changes according to the thrombosis and auto-thrombolysis mechanisms, regional vasomotor response, and global hemodynamic status.[4]

Non-contrast computed tomography (NCCT) is the first brain imaging study when a stroke patient was taken to the emergency room. It is useful to differentiate between hemorrhagic and ischemic stroke, with the former characterized by a spontaneously hyperattenuating area within the brain parenchyma representing fresh blood. During the first few hours, ischemic lesion is difficult to see in NCCT images. The early ischemic area detectable by in NCCT images usually represents irreversible ischemic core.[5]

"Time is brain" emphasizes the importance of restoring the blood flow of the occluded artery as fast as possible to save the viable brain tissues, that is, the penumbra. If a large ischemic core already formed and only a small penumbra is left, recanalization of the occluded artery is of little benefit, and may increase the risk of hemorrhagic transformation due to reperfusion injury. It is therefore important to

estimate the ischemic core and penumbra of stroke patients to decide whether the patient should receive the EVT or not.

Currently, the gold standard of brain perfusion is measured by positron emission tomography (PET) using radiotracer such as O^{15}. However, PET examination is difficult to be applied in clinical settings due to its high cost, difficulty in staffing and maintaining onsite cyclotron, and it has low spatial resolution. Therefore, more widespread imaging modalities, including the computed tomography perfusion (CTP) imaging and magnetic resonance perfusion (MRP) imaging, is commonly used for perfusion imaging studies. Because of limitations of both CTP and MRP, the perfusion parameters are usually not considered quantitative but rather normalized to a presumed normal reference region of the brain and expressed proportionately.[6]

Perfusion source data is a 4-dimensional data set (3-dimensional volumes captured over time). Using contrast media as tracers, the tracer kinetic models are used to estimate the hemodynamic parameters for each voxel, converting the 4-dimensional data set into perfusion maps that represent different hemodynamic properties. Computation of the perfusion maps is based on a relationship between the bolus shape in the feeding vasculature, the arterial input function, and the contrast passage observed in each voxel. Mathematically, this relationship is determined using a deconvolution algorithm which enables computation of perfusion parameters.[7]

In brain perfusion studies, the ischemic core is usually determined by cerebral blood flow (CBF), which can be calculated according to the following formula:

CBF = CBV/MTT

Where cerebral blood volume (CBV) is the amount of blood volume (cerebral blood volume, that is, vascularized, typically 2-5%), and mean transit time (MTT) is the average of time spent for the tracer to traverse the capillary bed. The ischemic core is usually defined as the brain regions with CBF <20% or <30%. To estimate the ischemic penumbra, the time to peak of contrast arrival (Tmax) > 6s or > 4s is used and provides reasonable estimates of final infarction in patients without reperfusion.[7]

Besides the perfusion imaging studies, the multiphase CT angiography (mCTA) is also applied to estimate the ischemic area. The display of mCTA consists of 3 sequential gray-scale images series of the cerebral vasculature to show the filling delay and pattern defect of the pial arteries at the affected brain area. Collateral status as determined by mCTA has been shown to correlate with the ischemic volumes in patients presenting beyond 6 hours. Compared with perfusion studies, mCTA study is less time-consuming and hence less prone to movement artifacts, and also less succumb to skull base artifacts and can therefore better visualize the posterior circulation.[8]

Multiple software products that estimate the location of LVO, perfusion maps, volumes of ischemic core and penumbra, and collateral status are available. However, the perfusion processing is a nonstandard domain and significant differences exist between vendors. Frequently, the CBF, CBV, and Tmax are calculated differently and therefore not comparable between packages. It is, therefore, recommended to use software that has been validated on clinical data sets where it is known to what extent estimated volumes are meaningful for clinical use.[9]

Subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH) are two

subtypes of hemorrhagic stroke. About 85% of SAH is due to the rupture of cerebral aneurysm. Cerebral aneurysms, however, often remain clinically silent for a long time and are incidentally found. The risk of aneurysm rupture can be predicted based on the morphology, size, location, and the local hemodynamic characteristics of the aneurysm. The treatments of aneurysm include traditional endovascular coiling and surgical clipping; in recent years, flow diverter is gaining popularity in treating some of the difficult-to-treat aneurysms.[10,11]

In this study, we have 3 main projects. The first project is to generate an artificial intelligence algorithm that can predict the tissue and clinical outcomes of stroke patients based on their baseline characteristics, time-related and time-independent stroke characteristics, and the mCTA and CTP acquired at the hyperacute stage of stroke. The second project is to explore the effects of chronic cerebral arterial stenosis on the measurements of the mCTA and CTP. The third project is to analyze the successful rates and complications of different treatment strategies for cerebral aneurysms.

Non-contrast Computed tomography (NCCT) and multiphase computed tomography angiography (mCTA)

NCCT was performed using a head holder in a 64-slice CT scanner (Lightspeed, General Electric Medical Systems) at the ER with the following scanning parameters: 120 kV, 250 mA, 4-s scan time, 5-mm section thickness, and coverage extending from the skull base to the vertex using contiguous axial sections parallel to the planum sphenoidale. In the mCTA protocol, mCTA was acquired immediately following NCCT. The first phase of mCTA acquiring images from the arch to the vertex took approximately 8 s. After a delay of 16 s, allowing the table repositioning to the skull base, the second phase was acquired. The scanning duration for each additional phase was 3 s, and the second and third phases were 8 s apart. A total of 38 s elapsed from the first phase to the third one. A total of 100 mL of contrast material (75% OMNIPAQUETM 350; General Electric Company, Norwegian) was injected at a rate of 2.5 mL/s. The 3-mm overlapping axial images were immediately reformatted, and thick-section axial maximum intensity projections (15-mm thickness and 3-mm intervals) were also reconstructed.

Computed tomography perfusion

CTP functional maps were processed using commercially available deconvolution software (CT Perfusion 4D; GE Healthcare). CTP was performed using the cine scanning mode (one image per second) with 80 kVp, 200 mAs, a 5-mm slice thickness, and total brain coverage of 40 mm. A 4-second scanning delay was used after the IV injection of 40 mL of nonionic contrast material (Isovue 370) at 4 mL/s, followed by 40 mL of saline solution. The gantry angle was selected to avoid radiation exposure to the orbits. The total scan time was 60 seconds. The inferior slice was selected at the level of the basal ganglia to include the vascular territory from the MCA and anterior and posterior cerebral arteries.

Infarct Segmentation and Perfusion Data Extraction

Delineation of the follow-up infarct volume (ROI-1) was performed on the

follow-up DWI by applying a single standardized intensity. A noninfarct ROI (ROI-2) encompassed any brain tissue outside ROI-1, including voxels from the contralateral hemisphere. Subcortical structures (ie, basal ganglia, including the caudate, lentiform, and internal capsule) were manually segmented and analyzed separately from cortical gray/white matter. Histograms were generated for all ROI-1 and ROI-2 segmentations, respectively, from the SPIRAL perfusion image and CTP Tmax and CBF maps because these maps have been previously shown by the authors to have the highest accuracy for final infarction. Patient-level histograms from ROI-1 and -2 were amalagamated to create a single "all patient" ROI-1 and ROI-2 to perform a cohort-level analysis.

Study populations

We retrospectively analyzed the stroke patients admitted to Chang Gung Memorial Hospital at Linkou from June 1 2015 to March 31 2022. Patients chart number are needed in order to review their imaging and clinical data in detail. Patients' data will be identified after data collection, and we will try our best not to disclose the data to the third party.

Patient data collection

1. The brain CT/mCTA/CTP/MRA imaging files.
2. Stroke severity and functional outcomes at admission and discharge, evaluated by the National Institutes of Health Stroke Scale (NIHSS), Barthel Index, modified Rankin Scale, Fugl-Meyer assessment, motor-activity log, European quality of life five-dimension questionnaire (Euro-QoL-5D), Instrumental activities of daily living scale (IADL), Berg Balance Scale (BBS), gait speed, 6-min walk test (6-MWT), Mini-Mental Status Examination (MMSE), and concise Chinese Aphasia Test (CCAT).
3. Initial biochemistry and hemogram tests (including sugar for Acute Stroke Registry and Analysis of Lausanne [ASTRAL] score calculation) at stroke onset.
4. Electrocardiogram (atrial fibrillation) and vital signs (heart rate, blood pressure, respiratory rate).
5. Onset-to-CTP duration (wakeup or non-wakeup stroke, witnessed or unwitnessed stroke), onset to recanalization duration, recanalization result (graded by Thrombolysis in Cerebral Ischemia [TICI] score), and EVT methods.
6. CTA or MRA findings before and after IV-tPA and EVT treatment. These includes the location (common carotid artery [CCA], internal carotid artery [ICA], MCA, PCA, vertebral artery [VA], basilar artery) and degree of vessel occlusion or stenosis, plaque morphology (calcification, ulceration, softness, enhancement, total plaque thickness), The Alberta Stroke Program Early CT Score (ASPECTS), multiphase CTA collateral score (range, 0-5, 0 indicates no visible vessel in the affected hemisphere, and 5 indicates no filling delay and normal pial vessels in the affected hemisphere compared with the contralateral side), presence of previous stroke lesion, the ischemic penumbra and ischemic core, plaque morphology (echogenicity, surface, IMT), final infarct volume as determined by diffusion restriction imaging (DWI).

7. Treatment strategies: stenting, endarterectomy, medication. (such as duration of DAPT before and after stenting)
8. Complications and restenosis rate at follow up after treatment.
9. Cardiac echo, neck and intracranial doppler examinations reports.

Project 1. Predict the tissue and clinical outcomes of acute stroke patients based on patients' clinical data and brain imaging studies

In this project, we processed the mCTA to generate SPIRAL perfusion functional map according to previous study.[12] We registered each phase of the mCTA to the NCCT using a rigid registration. The NCCT was used to determine the baseline Hounsfield unit for each region of the brain in a respective patient. The NCCT and dynamic series generated from the mCTA were postprocessed and registered on a brain CT template. Time attenuation curves were created for each voxel after subtraction of the baseline NCCT Hounsfield unit values. Deconvolution and nondeconvolution approaches were used to generate functional maps of TTP or T0 (time to peak of impulse residue function), CBF, MTT, and CBV. The patients' outcome at discharge and final tissue volume determined by brain MRA were compared with the ASPECTS scores, ischemic core and penumbra volumes estimated by our AI algorithm and by a commercial AI software, Stroke Viewer (Nico-lab, Amsterdam, Netherlands), which assess all important biomarkers on CT and has been approved by the United States Food and Drug Administration in 2020 that enables faster triaging of stroke patients for endovascular thrombectomy.

Outcome assessment

1. The sensitivity, specificity, and area under the receiver-operating curve (AUC) of our AI algorithm and Stroke Viewer in detecting stroke patients with and without LVO.
2. Reasons of false positive and negative in LVO prediction (e.g., chronic occlusion).
3. Compare the stroke volume estimated by Stroke Viewer and the final tissue outcome determined by magnetic resonance angiography or computed tomography angiography. (Explore the Tmax >6 volume / Tmax >2 volume).
4. Analyze the factors that may affect the estimated ischemic penumbra and core volume and lead to overestimation or underestimation of the final infarct volume, including patients' comorbidities, neuroanatomy (intactness of Circle of Willis, fetal type posterior cerebral artery [PCA]), stroke etiology (LVO, lacunar infarct, cardioembolism), onset-to-CTP, onset-to-recanalization time).
5. Analyze the recanalization rate of different EVT doctors.

Project 2. Perfusion imaging in patients with chronic large artery stenosis or occlusion

Commercial perfusion imaging software are known to be less precise in predicting the ischemic penumbra and ischemic core of stroke patients with chronic large artery stenosis. The possible explanations to the overestimations include the ischemic conditioning of the brain tissue and development of collateral pathways. In this project, we applied our AI algorithm and that of the Stroke Viewer in patients

with chronic large artery stenosis and analyzed the factors that may lead to overestimation or underestimation. Besides, we also analyzed the change in cerebral collateral and perfusion pattern for patients who underwent interventional treatment, such as stenting and carotid endarterectomy.

Project 3. Flow diversion of aneurysmal to prevent SAH

In this project, we aimed to investigate the outcomes of patients with aneurysm treated by various methods. Our primary interest is to analyze the outcome of asymptomatic ICA aneurysm treated by flow diverter.

Data collection

1. The morphology, location, size of the aneurysms
2. The methods of treatment (flow diverter, coiling, clipping).
3. The detail of the endovascular procedure, including the size of the flow diverter, location of deployment).
4. Complication during and after the procedure.
5. Duration and regimen of premedication and postprocedural medication.
6. Outcome of the aneurysm (total or partial obliteration, stable, enlargement).

Statistics

The receiver operating characteristic (ROC) curve will be generated by testing the estimated ischemic pixel and plotting the sensitivity versus false positive rate. Pixels with CBF below the threshold were classified as true positive if the pixel was DWI-positive, and false positive otherwise. Pixels with CBF equal to or above the threshold were classified as false negative if the pixel was DWI-positive, and true negative otherwise. Expert contoured follow-up infarct volume was used as reference standard to evaluate mCTA and CTP predicted core and penumbra volume in the test cohort. Bland-Altman plots were used to illustrate mean differences and limit of agreement between mCTA predicted and reference standard volumes. Predicted and reference standard volumes were also assessed using concordance correlation coefficient and intra-class correlation coefficient. Spatial agreement between predicted lesion and reference standard was assessed using Dice similarity coefficient. All statistical analyses were performed using MedCalc version 17.8 (MedCalc Software, Mariakerke, Belgium) and MATLAB R2018a (The MathWorks Inc., Natick, MA, USA). A two-sided alpha <0.05 was considered as statistically significant.

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