Clinical and radiological factors predict unexplained early neurological deterioration after intravenous thrombolysis in patients with acute middle cerebral artery stroke

Yiping Ding
First Affiliated Hospital of Soochow University
Tong Sun
First Affiliated Hospital of Soochow University
Yue Lu
First Affiliated Hospital of Soochow University
Shuangjiao Huang
First Affiliated Hospital of Soochow University
Shanshan Diao
First Affiliated Hospital of Soochow University
Tan Li
First Affiliated Hospital of Soochow University
Juehua Zhu
First Affiliated Hospital of Soochow University
Qi Fang
First Affiliated Hospital of Soochow Universit
Xiuying Cai
First Affiliated Hospital of Soochow University
Zhuan Xu
First Affiliated Hospital of Soochow University
Yan Kong (kong0919@163.com)
First Affiliated Hospital of Soochow University https://orcid.org/0000-0001-6599-2416

Research article

Keywords: multimodal CT, thrombolysis, middle cerebral artery stroke, early neurological deterioration

Posted Date: February 23rd, 2019

DOI: https://doi.org/10.21203/rs.2.404/v1

Abstract

Background Some patients with acute middle cerebral artery stroke (MCA-stroke) cannot benefit from thrombolysis and develop early neurological deterioration (END) within 24 hours. Except for several defenitive causes such as symptomatic intracerebral hemorrhage, malignant edema, and early recurrent stroke, no definitive mechanism (unexplained END) account for majority of END cases deserving our attention. Methods We retrospectively collected 142 MCA-stroke patients who had pretreatment multimodal CT including non-contrast CT (NCCT), CT angiography (CTA) and CT perfusion (CTP) and received intravenous thrombolytic therapy within 4.5h of onset and. Unexplained END was denited as NIHSS scores increased from baseline within 24 hours after thrombolysis ≥ 4 points or death without definite causes. The clinical and imaging data based on multimodal CT were compared between unexplained END and no END through univariate and multivariate regression analyses. Results The prevalence of unexplained END (24 patients, 16.9%) outnumbered the prevalence of END due to other causes. Univariate analysis showed that higher admission glucose (P= 0.039), lower initial NIHSS score (P=0.026), lower r-LMC score (P= 0.003), proximal occlusion (P=0.003) and large penumbra volume(P<0.001) were more frequently observed in patients with unexplained END; In multivariate analysis, lower NIHSS score (OR=1.19; 95% CI, 1.07-1.32; P=0.001), proximal occlusion (OR=0.32; 95% CI, 0.06-0.92; P=0.038), lower r-LMC score (OR=1.17; 95% CI, 1.02-1.35; P=0.028) and larger penumbra volume (OR=0.98; 95% CI, 0.96-0.99; P=0.003) were associated with unexplained END. Conclusion Lower NIHSS score, proximal occlusion, lower r-LMC score and larger penumbra volume can predict unexplained END in the hyperacute phase of MCA-stroke and contribute to develop treatment strategies.

Background

Acute ischemic stroke (AIS) is considered the leading cause of morbidity, disability and long-term physical disability worldwide, with features of the sudden loss of a part of the brain's blood supply, accompanied by corresponding neurological deficits, such as sudden hemiplegia and speech impairment with limited therapeutic options in the acute period of ischemia [1, 2]. As a recombinant tissue plasminogen activator (r-tPA), alteplase is the only first-line drug approved and recommended for the treatment of AIS in the time window throughout the world. Numerous clinical investigations have demonstrated the safety and efficacy of intravenous thrombolysis within 3-4.5 hours of symptom onset [3-5]. Despite this, some patients are unable to benefit from thrombolytic therapy or even experience early neurological deterioration (END) within 24 hours after intravenous thrombolysis, which not only offsets the benefits of intravenous thrombolysis, but also leads to the deterioration of neurological function, which is independently associated with poor prognosis at 3 months [6]. Estimates of the incidence of END after AIS varied from 5% to 40% in the available studies depend on the clinical definition and time frame used for the deterioration [7-9] . To date, an increase on the National Institutes of Health Stroke Scale (NIHSS) of four points or more within the first 24h has been utilized to define END in majority of recent publications [10]. Recent reviews indicated that about 13.8% of patients treated with intravenous rtPA experienced END employed the same definition [11]. In addition, several straightforward causes

account for END such as symptomatic intracerebral hemorrhage, malignant edema, and early recurrent stroke have been conformed in prior studies, and there is no definitive mechanism in 2/3 of END cases, which is defined as unexplained END [10, 12]. Unexplained END has only received widespread attention in non-thrombolysed AIS, relevant studies in thrombolysed AIS is scarce. In a study on the mechanism of END unexplained, Tisserand et al found that unexplained END was associated with an increase in the area of the ischemic penumbra in diffusion weighted imaging (DWI), the location was consistent with the adjacent infarct image at admission and there was no recanalization within 24h [13]. In a prospective study, Seners et al reported that prior antiplatelet therapy, lower admission NIHSS, hyperglycemia, larger mismatch volume, proximal arterial occlusion, and lack of recanalization were frequently associated with unexplained END[10]. However, the long scan time, the existence of contraindications, and the difficulty of performing magnetic resonance (MR) in many hospital emergency departments have limited the application of MR. Relatively speaking, the advantages of shorter scan time, easier tolerance and coordination, and easier monitoring make multi-mode CT widely used. The aims of this study were to identify the value of radiological factors based on multi-mode CT for predicting unexplained END within 24 h after IV rt-PA therapy, which is of great significance for preventing the development of unexplained END in hyperacute period, effectively treating the unexplained END that has occurred and improving the prognosis of patients with acute ischemic stroke.

Methods

This study retrospectively collected AIS patients who received intravenous thrombolytic therapy with alteplase (Boehringer Ingelheim, Germany) within 4.5 of the onsets of neurology in the First Affiliated Hospital of Soochow University from August 2016 and September 2018. Patients were included in present study if they (1) are middle cerebral artery (MCA) stroke (2) had pretreatment multimodal CT including non-contrast CT (NCCT), CT angiography (CTA) and CT perfusion (CTP). Then we excluded the following patients: (1) modified Rankin scale core (mRS) > 1, (2) received subsequent endovascular treatment combined with intravenous thrombolysis, (3) had no abnormal ischemia perfusion on CTP associated with clinical symptoms. According to the current European guidelines (except for age > 80 years old), the decision of IV-rtPA treatment is determined by an experienced stroke neurologist. The stroke severity of all patients was assessed using the NIHSS before and at 2 h, 24 h and progressive onset of neurological deterioration after IV-rtPA administration. All patients underwent emergency NCCT, multimodal CTA and CTP to assess blood flow and perfusion status in patients with thrombolysis during the hyperacute phase. We divided patients into END and no-END groups according to whether END occurred after thrombolysis (NIHSS scores increased from baseline within 24 hours after thrombolysis) ≥ 4 points or cause death). Follow up Magnetic resonance imaging (MRI) or CT was performed during 24 h after IV rt-PA thrombolysis in all patients. The baseline data such as demographic, clinical, and imaging data at the time of patient presentation were gathered.

Definition and Etiologic Classifications of END

In the present study, END was utilized to define a NIHSS exacerbation of 4 points or more at any time point within 24 hours after thrombolysis, including neurological deterioration compared to optimal neurological status after thrombolysis [14]. Symptomatic hemorrhage is defined as parenchymal hemorrhage type 2: an increase of four points or more on NIHSS combined with a mass effect conformed by CT or MR imaging obtained at time of worsening according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria [15]. Early malignant edema is considered when neurological function deteriorates along with the progression of edema in initially infarcted tissue with obvious mass effects and midline shift without hemorrhage from follow-up imaging [16]. Early recurrent ischemic stroke is defined as the occurrence of new infarctions in an independent arterial region, which is clinically and visually confirmed and excludes an explanation for the increased degree of neurological deficits due to arterial re-occlusion or emboli extension [17]. END without any of the above reasons is defined as unexplained END.

Neuroimaging Protocol

All patients had a non-contrast CT scan, multimodal CTA and CTP of head/ neck at admission. The details about imaging acquisition are as previous studies [18].

CTP image post processing

FastStroke, an automated image postprocessing system, was employed to calculate the volume of the penumbral and ischemic core from CT perfusion scans. The size of the penumbra was estimated from the volume of tissue for which there was delayed arrival of an injected tracer agent (time to maximum of the residue function [Tmax]) exceeding 6 seconds. (An example is given in Fig. 1.)

CTA image analysis

CTA diagnosis criteria for Internal Carotid Artery (ICA) stenosis: The degree of carotid stenosis was calculated according to the measurement criteria used in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [19]. Formula: Stenosis rate (%) = (normal ICA diameter in the distal segment – minimum residual diameter in the stenosis segment) / normal ICA diameter in the distal segment × 100%. Divided into 4 groups according to the degree of carotid stenosis: mild stenosis<50%), moderate stenosis (stenosis rate 50 to 69%), severe stenosis (stenosis rate 70% to 99%), complete occlusion. 30 mm maximum-intensity projection (MIP) images were reconstructed in axial, sagittal and coronal planes. The diagnosis of CTA images was performed by two experienced radiologists.

ASPECT score

Alberta Stroke Program Early CT (ASPECT) scores were assigned by a single baseline blinded vascular neurologist who reviewed al baseline non-contrast CT scans. And the ASPECT score was performed as described previously [20].

The rLMC Score

The leptomeningeal collaterals were assessed employing the regional leptomeningeal collateral (rLMC) score on baseline CTA [21]. The rLMC score is based on the pia and lenticulostriate arteries (0, no difference; 1, less prominent than the corresponding region in the opposite hemisphere; 2, equal or more prominent than the matching region in the contralateral hemisphere) in 6 ASPECTS area (M1-M6) plus anterior cerebral artery region and basal ganglia. The pial arteries in the Sylvian sulcus scored 0, 2 or 4 (0, unobserved; 2, less prominent compared to the opposite Sylvian sulcus; 4, equal or more prominent than the opposite Sylvian sulcus).

Statistical Analysis

All statistical analyses were performed using SPSS 24.0 software (IBM SPSS, USA). Measurement data is expressed by the mean ± standard deviation (x±s), and the skewed distribution measurement data is expressed by the median (quartile); the count data is expressed by the number of cases (%). The baseline data comparison between the two groups was firstly analyzed by single factor analysis. The measurement data in accordance with the normal distribution were compared using two independent samples of the t test. The measurement data that did not conform to the normal distribution were compared using the Mann-Whitney U test of two independent samples. The count data was compared using the Pearson chi-square test or the continuously corrected chi-square test or Fisher's exact probability method. Baseline variables comparing P values <0.05 between the two groups were included in the logistic regression equation, and the multivariate analysis was performed by backward stepwise remove of the LR method to explore the risk factors for predicting END after thrombolysis. A two-tailed P value <0.05 indicates a statistically significant difference.

Results

In this study, a total of 309 patients with anterior circulation infarction were enrolled, 99 of whom were excluded because they are not MCA-strokes. Of the remaining 210 MCA-strokes, 46 were excluded because they received rt-PA intravenous thrombolysis combined with endovascular therapy, 164 patients only received intravenous thrombolysis. Of those, 22 cases were excluded for the following reasons: 1. lack of CTA and CTP imaging because multi-mode CT examination was not performed before thrombolysis; 2. unavailable or insufficient quality CTP; 3. without 24h-NIHSS assessment. Finally, 142 patients were included for the present analysis, with 34 patients (23.9%) experiencing END. The prevalence of unexplained END patients (24 patients, 16.9%) outnumbered the prevalence of patients with END due to symptomatic intracranial hemorrhage (sICH) (8 patients, 5.6%) and early swelling (2 patients, 1.4%). No patient deteriorated because of early recurrent ischemic stroke. Table 1 presents the baseline characteristics and radiologic features of the studied population with unexplained END and No END.

Univariate Analysis of Predictors

Table 1 presents the results of univariate analyses related to the clinical and radiological data of patients with unexplained END and without END. As shown in Table 1, no vascular risk factor (age, previous

stroke, hypertension, diabetes, hyperlipidemia, atrial fibrillation, or current smoking) identified patients at risk for unexplained END in our univariate analyses. Furthermore, the prior medication including the use of antiplatelet, statin, antihypertensive drugs did not statistically affect the deterioration of neurological function. There were no statistical differences in diastolic or systolic blood pressure, white blood cell (WBC), low density lipoprotein (LDL), high density lipoprotein (HDL), total cholesterol (TC), uric acid (UA), platelet (PLT), international standard ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrin degradation products (FDP) and serum creatinine (Scr) between the two groups. The higher admission glucose (P= 0.039), lower initial NIHSS score (P=0.026), lower r-LMC score (P= 0.003), proximal occlusion (P=0.003) and large penumbra volume (P<0.001) were more frequently observed in patients with unexplained END in comparison to patients without END group.

Multivariate Analysis of Predictors

Baseline variables with P value <0.05 including the higher admission glucose (P= 0.039), lower initial NIHSS score (P=0.026), proximal occlusion (P=0.003), r-LMC score (P=0.003), penumbra volume (P<0.001) in the univariate analysis were all included in the multivariate logistic regression. With the final model, lower NIHSS score (OR=1.19; 95% CI, 1.07-1.32; *P*=0.001), proximal occlusion (OR=0.32; 95% CI, 0.06-0.92; *P*=0.038), lower r-LMC score (OR=1.17; 95% CI, 1.02-1.35; *P*=0.028) and larger penumbra volume (OR=0.98; 95% CI, 0.96-0.99; *P*=0.003) were associated with unexplained END.

Discussion

Patients with acute ischemic stroke may experience more severe neurological deficits after intravenous thrombolysis due to a variety of causes such as symptomatic intracranial hemorrhage, early swelling, early recurrent stroke, and unexplained END meaning no clear mechanism is found. Furthermore, the unexplained END accounts for about 2/3 of all causes of END [10]. How to identify unexplained END and take effective measures to prevent its occurrence and development in the acute phase is essential for improving prognosis. This study was the first to use multimodal CT to assess risk factors for unexplained END in the hyperacute phase of stroke in order to prevent stroke progression.

Our study demonstrated that incidence of END was 23.9%, which is consistent with the prevalence of 8.1–28.1% when focusing on the most widely used ΔNIHSS ≥4 definition within 24h after IV-rtPA based on previous conclusions [11]. Especially, unexplained END accounted for about 70% of all causes END, seemed to be a major contributor to END after thrombolysis, which is in line with the incidence of 2/3 in prior investigations. Furthermore, it occurs approximately 3 times as frequently as symptomatic intracranial bleeding in present study, similar to the recent evidence that also aimed at unexplained END after thrombolysis in MCA stroke [10]. None of the patients deteriorated due to early recurrent ischemic stroke in our study, which is in accordance with low incidence previously reported [22, 23]. It is worthy of our attention that, as the major cause of END after thrombolysis, the prevalence and characteristics of unexplained END within 24 hours after thrombolytic treatment have not get enough emphasis in comparison to hemorrhagic complications. Previous literature reports that, in the case of persistent

occlusion of the proximal vessel and extensive mismatch of DWI-PWI, the destruction of local perfusion pressure secondary to in situ thrombosis or distal migration of the thrombus accompanied with hyperglycemia during ischemic episodes possibly contribute to explain the mechanism of unexplained END [13]. Our study incorporates clinical and multimodal CT-based imaging risk factors that may be relevant to the above mechanisms to quickly and accurately assess unexplained END in the hyperacute phase to guide subsequent treatment.

Our analysis showed that a strong predictor of unexplained END is the lower admission NIHSS score. Lower initial NIHSS associated with proximal occlusion generally indicate early deterioration in increasingly reported researches [14]. NIHSS score focuses on the neurological deficits but it can not reflect the intracranial and extracranial vascular and brain perfusion status. Multimodal imaging studies suggest that some minor stroke patients with symptomatic intracranial and extracranial arterial stenosis or occlusion usually have obvious hypoperfusion areas in the acute phase and tend to develop into an imaging infarction progression in acute phase indicating poor prognosis [24, 25].

Evidences from previous publication that the higher admission blood glucose is related to unexplained END [10], the mechanism involves: 1. Higher glycemia exacerbates the anaerobic glycolysis and facilitates conversion of hypoperfused at-risk tissue into infarction [26] ; 2. Hyperglycemia is not conducive to the establishment of new collateral circulation in the infarction site [27]; 3. Elevated glucose delays reperfusion of the ischemic penumbra in stroke patients treated with rtPA and facilitates thrombus extension due to the antifibrinolytic effect [28]. However, there was no statistically difference in blood glucose levels between the no END and unexplained END groups in our multivariate Analysis. This phenomenon can be explained as follows: many patients with admission hyperglycemia received insulin hypoglycemic therapy. The lack of 24-hour dynamic blood glucose monitoring resulted in no significant difference between the two groups.

Multimodal CT including NCCT, CTA and CTP, gradually being frequently applied and have shown distinguished potential for predicting prognosis and selecting therapeutic strategy due to its rapid acquisition, relatively low expenditure and acceptable tolerance, it is increasingly being utilized in emergency AIS patients [29]. CTA and CTP parameters are capable of providing crucial information about intracranial occlusion, collateral circulation, and infarct cores that differentiate penumbra from the irreversibly infarct core [30].

Our statistics indicated the poor collateral circulation based on CTA is a predictor of unexplained END. As we all know, cerebral collateral circulation is a network of arterial anastomotic channels which are capable of outwardly remodeling so as to provide additional supplemental perfusion to brain tissue that encounters ischemic insults [31, 32]. Abundant collateral circulation is contributed to increase the occurrence of recanalization in patients received thrombolytic therapy [33, 34]. The potential theoretical explanations possibly involve rich collateral vessels are more beneficial to the dissolution of endogenous fibrin and transport of thrombolytic agents will therefore promote the recanalization of blood vessels [35]. Additionally, patients with poor collaterals and/or insufficient vascular structure will have longer

thrombus extension into the pial arteries and increased clot burden, thus resulting in reduced recanalization of intravenous tPA [36]. It has gained widespread acceptance that proximal occlusion is the best predictor for END [37], findings which was confirmed again in our studies.

Proximal occlusion bears a greater burden of thrombosis due to the larger volume of thrombus and increased difficulty in dissolution [38]. In addition, responsible large vessel occlusion leads to short-term blood flow reduction, insufficient distal blood vessel perfusion, ischemia and hypoxia of large area of brain tissue, all of which are detrimental to the rescue of the ischemic penumbra [39]. Finally, studies have shown that the infarction site of progressive stroke is more common in the watershed area of the large vessel and the side of the lateral ventricle, which may be related to the difficulty in establishing a rich collateral circulation after infarction [33]. The above reasons are not conducive to the successful recanalization of blood vessels after thrombolysis, which may lead to the occurrence of unexplained END.

Responsible large vessel stenosis or occlusion is generally accompanied by large hypoperfused volumes. Penumbra, a salvable hypoperfused zone, the presence of which usually means a better response to IV tPA and symptom relief [12]. However, alteplase has limited effect on intravenous thrombolysis of large vascular occlusions such as internal carotid artery and middle cerebral artery, resulting in poor revascularization, and the penumbra cerebral blood flow continues to decrease and eventually develop into infarction [38]. This suggests that penumbra may help predict END. Previous conclusion that larger DWI–PWI mismatch volume was associated with unexplained END further support our investigation.

This study has certain limitations. First, this study is a single-center study in a single city. The characteristics of local populations tend to be biased. The results should be further confirmed by other cohort studies. Secondly, this is a retrospective study. Although some confounding factors are corrected, it is inevitable that there will be selection bias in the enrolled patients and recall bias in some clinical situations. Therefore, prospective cohort studies of pre-existing exposures are needed to verify the conclusions. Additionally, physiological data such as blood pressure drops or swings, hyperglycemia changes during first 24 h is insufficient, which was related to the neurological status 24 hours after thrombolysis.

Conclusions

Taking together all the above findings, lower NIHSS score, imaging data based on multimodal CT including proximal occlusion, poor collateral circulation, and larger penumbra volume are significantly associated with unexplained END after intravenous thrombolysis in present study. It is recommended that patients with suspected risk factors should be given full attention and effective measures such as endovascular treatment should be taken as soon as possible to achieve safe and effective treatment for patients with AIS.

Abbreviations

Acute ischemic stroke (AIS); ASPECT: Alberta Stroke Program Early CT ; AF: atrial fibrillation; APTT: activated partial thromboplastin time; CT: Computed tomography; CTA : CT angiography; CTP: CT perfusion; DWI: Diffusion weighted imaging; END: Early neurological deterioration; FDP: fibrin degradation products; HDL: high density lipoprotein; INR: international standard ratio; LDL: low density lipoprotein; MR: Magnetic resonance; mRS: modified Rankin scale core; MCA: Middle cerebral artery; NCCT: non-contrast CT; National Institutes of Health Stroke Scale (NIHSS); OTT, onset-to-treatment time; PT: prothrombin time; PLT: platelet; r-tPA :recombinant tissue plasminogen activator; rLMC: regional leptomeningeal collateral ; Scr: serum creatinine; TC: total cholesterol; TOAST: Trial of Org 10 172 in acute stroke treatment. UA: uric acid; Unexplained END: early neurological deterioration without clear mechanism; WBC: white blood cell;

Declarations

Ethics approval and consent to participate

Institutional Review Board of The First Affiliated Hospital of Soochow University approved a request to waive of informed consent because it is not practicable to obtain consent from large numbers of patients for a retrospective chart review study, generally it also will not be appropriate to attempt to contact those patients to tell them about the study retrospectively. This study was approved by the The First Affiliated Hospital of Soochow University.

Consent for publication

Not applicable

Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study. The data that support the findings of this study are available from Department of Neurology, The First Affiliated Hospital of Soochow University, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Department of Neurology, The First Affiliated Hospital of Soochow University.

Competing interests

The authors declare that they have no competing interests.

Funding

This work supported by a grant from National Key R&D Program of China (2017YFC0114300), the National Basic Research Priorities Program of Jiangsu Province (Grant No. BK20160347), Jiangsu Province's Key Provincial Talents Program (Grant No. QNRC2016730) and Health and Family Planning

Commission of Jiangsu Province (Grant No. Z2017011), Suzhou Science and Technology Development Plan (Grant No. SYS2018043)
The fund body took no part in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Authors' Contributions

YK and ZX conceived and designed the study, including quality assurance and control, drafting the manuscript and revising it critically. YPD performed the study's analytic strategy and wrote the paper. TS and YL are responsible for the acquisition, analysis and interpretation of data. SJH, SSD, TL and JHZ participated in the acquisition of data and revision of the manuscript. QF and XYC helped conduct the literature review and prepare the Materials and Methods section of the text. All authors read and approved the manuscript.

Acknowledgments

None.

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Tables

The tables are attached as supplemental files due to technical limitations.

Figures

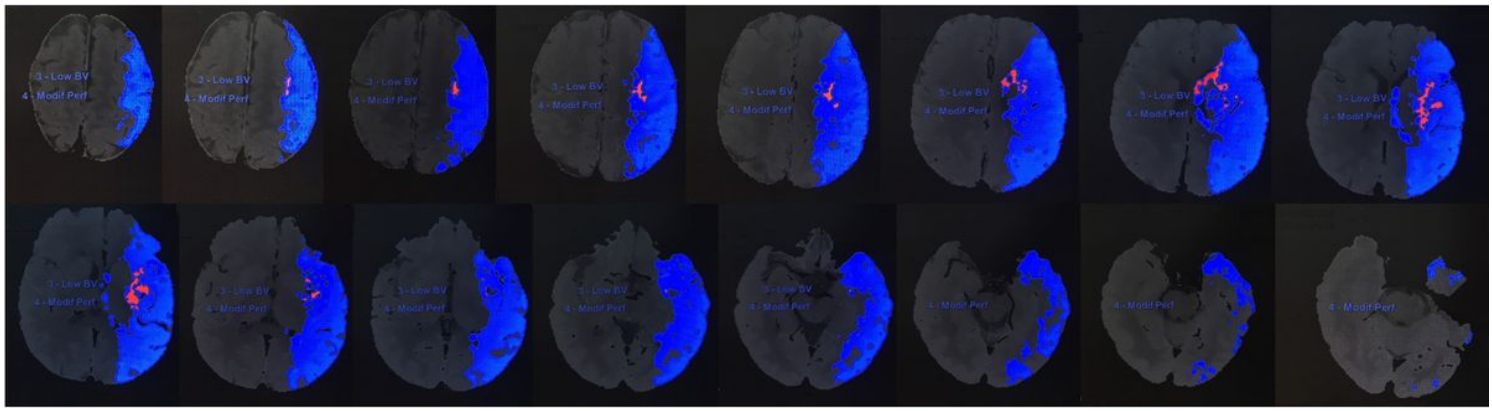

Figure 1

Example of perfusion imaging based on Multimodal CT. A patient (60-64 years old) was suddenly unconscious for 2 hours and 15 minutes. The admission NIHSS score is 22. CTA showed the occlusion of M1 of middle cerebral artery. The CTP images were obtained by post-processing with FastStroke software showing the volume of ischemic core (red) is 8.84cm3, volume of perfusion lesion (blue) is 153cm3.

Supplementary Files

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