Original Article

Multimodal CT imaging characteristics may predict post-reperfusion infarct volume in wake-up stroke patients

Arman Sha[1,2]^, Fan Yu[1,2], Miao Zhang[1,2], Yi Shan[1,2], Daode Guo[1,2], Milind Ratna Shakya[1,2]^, Xuesong Bai[3,4], Qingfeng Ma[5], Liqun Jiao[3,4,6], Jie Lu[1,2]^

[1]Department of Radiology and Nuclear Medicine, Xuanwu Hospital, Capital Medical University, Beijing, China; [2]Beijing Key Laboratory of Magnetic Resonance Imaging and Brain Informatics, Beijing, China; [3]Department of Neurosurgery, Xuanwu Hospital, Capital Medical University, Beijing, China; [4]China International Neuroscience Institute (China-INI), Beijing, China; [5]Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing, China; [6]Department of Interventional Neuroradiology, Xuanwu Hospital, Capital Medical University, Beijing, China

Contributions: (I) Conception and design: A Sha; (II) Administrative support: J Lu; (III) Provision of study materials or patients: A Sha, F Yu, M Zhang, Y Shan, D Guo, X Bai, Q Ma, L Jiao; (IV) Collection and assembly of data: A Sha, F Yu; (V) Data analysis and interpretation: A Sha, F Yu, M Zhang, MR Shakya; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jie Lu, MD, PhD. Department of Radiology and Nuclear Medicine, Xuanwu Hospital, Capital Medical University, Changchun Street, No. 45, Beijing 100053, China; Beijing Key Laboratory of Magnetic Resonance Imaging and Brain Informatics, Beijing 100053, China. Email: imaginglu@hotmail.com.

Background: Accurate prediction of subsequent infarct volume in acute ischemic stroke (AIS) patients helps determine appropriate interventions and prognosis. The objectives are to assess whether early multimodal CT imaging characteristics of wake-up stroke (WUS) patients could predict post-reperfusion infarct volume and evaluate the accuracy of baseline infarct and penumbra volumes for predicting follow-up infarct volume.

Methods: This retrospective study included WUS patients, last seen well (LSW) >6 h, with multimodal CT imaging at baseline. Baseline non-contrast CT (NCCT) and CT perfusion were analyzed using RAPID software, and CT angiography using maximum intensity projection. Post-reperfusion infarct volume was assessed at 24-h following reperfusion on magnetic resonance diffusion-weighted imaging (DWI). Patients were stratified by treatment module for analyses.

Results: Of 34 eligible patients, 9 (26.5%) received intravenous recombinant tissue plasminogen activator (r-tPA) alone and 25 (73.5%) received both endovascular thrombectomy (EVT) and r-tPA. All patients had a strong correlation between baseline NCCT alberta stroke program early CT score, clot burden score (CBS), Tan score, infarct volume, penumbra volume with 24-h post-reperfusion infarct volume (respectively, r=0.172, P=0.015; r=0.118, P=0.047; r=0.149, P=0.024; r=0.311, P=0.001 and r=0.120; P=0.045). Among reperfusion therapies, WUS patients who received EVT had a significantly lower 24-h post-reperfusion infarct volume and had a significant difference between baseline infarct volume and 24-h post-reperfusion infarct volume (respectively, 82 *vs.* 14, P=0.032 and 47 *vs.* 14, P=0.04).

Conclusions: Primarily obtained multimodal CT imaging characteristics may predict post-reperfusion infarct volume in WUS patients, and those who underwent EVT had a significantly lower post-reperfusion infarct volume.

Keywords: Acute ischemic stroke (AIS); wake-up stroke (WUS); CT perfusion; endovascular thrombectomy (EVT)

^ ORCID: Jie Lu, 0000-0003-0425-3921; Arman Sha, 0000-0001-9912-1678; Milind Ratna Shakya, 0000-0001-7384-9388.

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Introduction

Intra-arterial occlusion in acute ischemic stroke (AIS) forms irreversibly damaged tissue that cannot recover in the event of reperfusion called infarct core, and tissue at risk for infarction called the ischemic penumbra (1). Rapid reperfusion in AIS patients is essential to reduce the risk of disability and mortality (2). Endovascular thrombectomy (EVT) is the standard of care for AIS patients with proximal anterior circulation occlusions, which rescue the penumbral tissue (3). Wake-up stroke (WUS) is a subgroup of AIS in which patients sleeps in healthy condition while wake-up in the morning with new stroke symptoms, and it consists of around 25% of all AIS (4). Time of onset is unknown in WUS. The duration is nearly from 7 to 14 h from last time seen well to symptom noticed (5). Thus, WUS is conventionally classified into the late-time window, and the current guideline suggests complete multimodal imaging to assess EVT candidates (3). Either multimodal magnetic resonance imaging (MRI) or CT has been used to define potentially salvageable ischemic cerebral tissue in WUS (3). Multimodal CT is more often available, faster, cheaper, has fewer contraindications than MRI, and patients tolerate it better. Some study shows multimodal MRI overestimated ischemic penumbra (6,7).

The area of the tissue that rapidly undergoes irreversible injury is called the infarct core, and the peripheral region that contains tissue that may be salvaged is the ischemic penumbra. This penumbra can be salvaged with the quick establishment of the appropriate therapy (8,9). The consequence of AIS is clinical deficits, one of the final pathologic steps, which is direct measured by Infarct volume (10). Therefore, it is a surrogate marker to a classic disability or handicap scale (11,12), and to identify the candidate who got potential benefits of therapy (13). Furthermore, infarct volume is considered the fate of penumbra (14). In AIS patients, the prediction of infarct volume is difficult as ischemic lesions progress over time in response to numerous variables, including the timing and degree of reperfusion achieved and the adequacy of collateral circulation and following EVT (15-17). Previous study shows that baseline infarct and penumbra volume can predict infarct volume on follow-up imaging in AIS patients (18,19). However, very few studies addressed the role of baseline multimodal CT imaging in predicting infarct volume on follow-up imaging in WUS patients.

Therefore, this study aimed: (I) to assess baseline multimodal CT imaging characteristics and post-reperfusion infarct volume on follow-up diffusion-weighted imaging (DWI) of WUS patients; (II) to investigate the association of baseline multimodal CT imaging characteristics with post-reperfusion infarct volume on follow up DWI in WUS patients; (III) to compare WUS patients infarct volume at baseline and at post-reperfusion stratified by treatment module for analyses. We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-614/rc).

Methods

Study population

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Our institutional review board reviewed and approved this study, and written informed consent was obtained from each patient. All patients were retrospectively enrolled at Xuanwu Hospital, Capital Medical University, Beijing, China from January 2021 to January 2022. Neuroimaging was conducted for each subject at least 2-time points: (I) at baseline during admission and (II) at 24-h after reperfusion therapies. The site used multimodal CT imaging at admission and MRI at 24-h after reperfusion therapies. For reperfusion therapies of all WUS patients current guideline was followed (3).

Multimodal CT such as non-contrast CT (NCCT), CT perfusion (CTP) and CT angiography (CTA) was performed with suspected to have large vessel occlusion (LVO) in AIS patients. The inclusion criteria were: (I) suspected AIS within 24-h from the last seen well (LSW); (II) patients with AIS wake up with neurological deficits and LSW over 6-h; (III) CTA showing LVO in the anterior circulation from the intracranial internal carotid artery (ICA) to the M2-branch of the middle cerebral artery (MCA). Patients with stroke mimic on NCCT, intracranial

haemorrhage, contrast allergy, posterior circulation lesions were excluded, and known renal dysfunction. Demographic and clinical characteristics of WUS such as age, gender, LSW, NIHSS scores at admission, and modified rankin scale (mRS) scores at admission were collected.

Although the current guideline for WUS patients beyond the treatment window is ambiguous, in our center we are following current AHA guidelines for treatment (3). Criteria for WUS patient selection for EVT were as follows: (I) age <80 years old; (II) admission NIHSS ≥10; (III) baseline NCCT alberta stroke program early CT score (ASPECTS) ≥5; (IV) baseline infract volume on CTP is <70 mL; (V) baseline mismatch volume on CTP is ≥15 mL.

The decision to select patients who underwent for MRI was determined by the discussion between the clinical physicians and radiologists. Factors considered included (I) patient's or patient's relative's choice to undergo MRI, (II) patients tolerate MRI, and (III) absent of any contraindications.

Imaging protocol

A third-generation CT scanner (Revolution CT, GE Healthcare, UK) was used to perform whole-brain CTP and CTA of the cervical and cerebral artery acquisitions. The CTP was acquired using a tube current of 100 mAs, tube voltage of 70 kVp, collimation of 192×0.625 mm, gantry rotation time of 0.5 s, and coverage in the z-axis of 114 mm. Through antecubital vein 40 mL of iodinated contrast material (ioversol 370 mg/mL) was injected at a rate of 6 mL/s. Followed by 40 mL of saline at 6 mL/s was used for flushing, and scanning started 5 s after the injection. The dynamic perfusion scan consisted of 22 slices of images, each with 5 mm thickness. The CTA was acquired using a tube current of 200 mAs, tube voltage of 90 kVp, matrix of 512×512, from the aortic arch to calva. 50 mL of intravascular bolus contrast medium injected followed by 50 mL of saline were also administered at a rate of 5 mL/s in all patients. Scanning started 2 s after the monitor region of the aorta triggered the threshold of 100 Hu. The CTA scan was at 0.625 mm slice thickness and at 5 mm was reconstructed.

A 1.5 Tesla MRI scanner (Ingenia, Philips Medical Systems) with an 8-channel receiver array head coil was used to perform MRI examinations, and parallel imaging was employed. The detailed imaging parameter of DWI was as follows: echo planar imaging (EPI) techniques, TR, 2,454 ms; TE, 80 ms; FOV, 200 mm*232 mm, and section thickness, 5 mm. The b values of 0 and 1,000 s/mm^2 were used to obtained DWI.

Imaging evaluation

All imaging data were analyzed consensually by 2 radiologists, who had at least 3 years of experience in this field and were blind to the present study; and discussed to reach an agreement as required.

Multimodal CT imaging analysis

Several studies have demonstrated that ischemic core volume estimations varied significantly between different software packages, and the ischemic core volume on RAPID was most closely correlated with the final infarct volume (20-24). The DAWN and DEFUSE 3 trials selected patients based on ischemic core volumes estimated with RAPID software (iSchemaView, Menlo Park, CA, USA) (25,26). Therefore, in this study NCCT and CTP were analyzed automatically by using RAPID software (iSchemaView, Menlo Park, California, USA). On NCCT, early ischemic change of the brain was assessed by alberta stroke program early CT score (ASPECTS) (27), higher the score is better. On CTP, a relative cerebral blood flow (CBF) threshold of 30% was used to distinguish penumbra from infarct, and Tmax >6 s for the total ischemic area in software and quantified penumbra and infarct volume within the whole scan range (28,29). CTA was used to evaluate intracranial thrombus location and assessed clot burden score (CBS) (30). Higher the CBS is better. Tan score collateral filling was categorized as 0= vessels are absent than those on the contralateral side; 1= vessels are <50% filling than those on the contralateral side; 2= vessels are 50–<100% filling than those on the contralateral side; 3= vessels are 100% filling than those on the contralateral side (30), and the good collateral filling was defined as 2–3.

DWI analysis

Post-reperfusion infarct volume was quantified by using a semi-automated lesion segmentation tool ITK-SNAP (version: 3.8) (31). The edge of the DWI abnormality using the trace of the diffusion coefficient was identified visually. The region of interest was manually segmented into individual slices, and the infarct volume was obtained through automated summation of the values obtained at different slices.

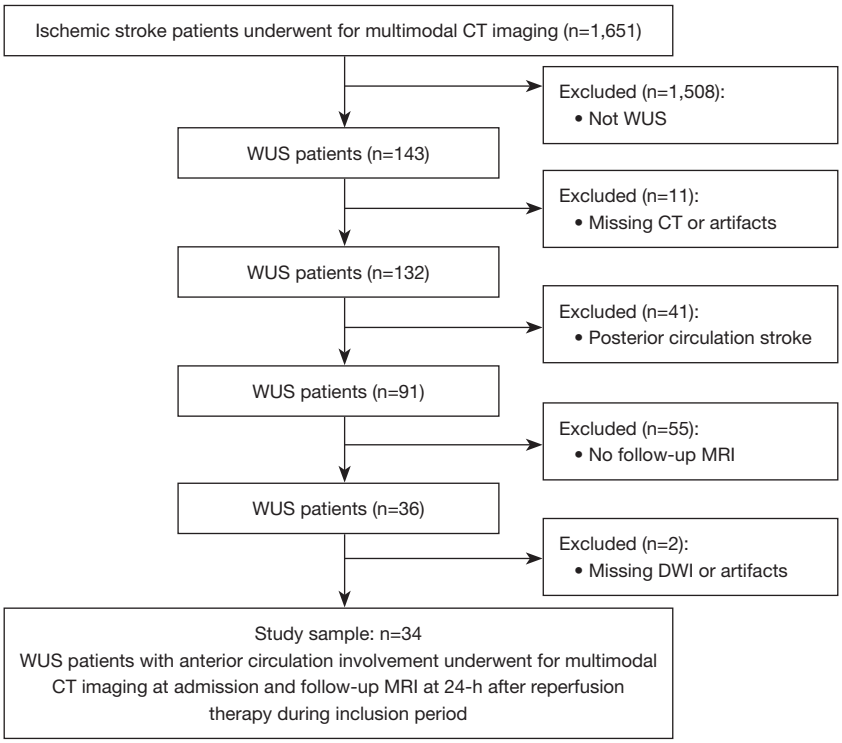

Figure 1 Flow chart of patient selection. WUS, wake-up stroke; MRI, magnetic resonance imaging; DWI, diffusion weighted imaging.

Statistical analysis

For calculations, IBM SPSS statistics version 26 was used. (I) Continuous variables were presented as median IQR. Categorical variables were presented as percentages. Continuous variables were analyzed with the Student *t*-test or Mann–Whitney U test according to their normality of distribution. Categorical variables were analyzed with χ^2 or Fisher exact tests; (II) Pearson correlation coefficient was used to correlate different baseline multimodal CT imaging findings, and post-reperfusion infarct volume; (III) Linear regression model was used to predict the post-reperfusion infarct volume; (IV) Bland-Altman analyses of agreement (32) were executed to illustrate the effectiveness of our linear models and whether the predicted post-reperfusion infarct volume tended towards overestimation or underestimation. A value of $P<0.05$ was considered statistically significant.

Results

A total of 1,651 patients came to the hospital with AIS symptoms during the study period (*Figure 1*). Among them, only 143 patients were WUS. Then, 132 WUS patients had multimodality CT imaging data. Ninety-one WUS patients were found with occlusion of the ICA or MCA (M1 and M2 segment). Thirty-six patients underwent follow-up MRI. Two patients were excluded due to missing DWI and significant artifacts. Ultimately, 34 patients were included in this study. Of these, 9 (26.5%) received intravenous recombinant tissue plasminogen activator (r-tPA) alone and 25 (73.5%) received both EVT and r-tPA. A total of 6 (17.6%) patients developed haemorrhages following reperfusion therapy. In all 25 patients in the endovascular arm, early endovascular reperfusion was achieved score of 2b–3 by thrombolysis in cerebral infarction (TICI) reperfusion during the procedure. *Table 1* summarizes baseline clinical characteristics, and *Table 2* summarizes imaging characteristics of all included WUS patients.

The slope of regression line between the admission NCCT ASPECTS and the 24-h post-reperfusion infarct volume (*Figure 2A* and *Table 3*) was −15.53 (95% CI: −27.797 to −3.263; r=0.172; P=0.015). The regression line for the relationship between baseline CBS (*Figure 2B*) and Tan score (*Figure 2C*) with 24-h post-reperfusion infarct volume had a slope of respectively, −9.5 (95% CI: −18.854 to −0.136; r=0.118; P=0.047) and −31.02 (95% CI: −57.665

Table 1 Baseline clinical characteristics of all included WUS patients

Variables	All patients (n=34)
Sex, male, n (%)	21 (61.8)
Age, year (IQR)	63 [56–70]
Symptoms noticed, mean ± SD, min	282.44±176.44
Last seen well, mean ± SD, min	628.91±236.82
NIHSS at admission (IQR)	13 (10–17.5)
mRS at admission (IQR)	0 (0–4)
H/O previous stroke, n (%)	3 (8.8)
H/O atrial fibrillation, n (%)	4 (11.8)
H/O diabetes mellitus, n (%)	7 (20.6)
H/O hypertension, n (%)	24 (61.5)
H/O dyslipidemia, n (%)	3 (8.8)

WUS, wake-up stroke; IQR, interquartile range; SD, standard deviation; NIHSS, national institutes of health stroke scale; mRS, modified rankin scale; H/O, history of.

Table 2 Imaging characteristics of all included WUS patients

Variables	All patients (n=34)
Side of the lesions, right, n (%)	16 (47.1)
NCCT ASPECTS (IQR)	7 [5–8]
Infract volume, mean ± SD, mL	17.76±25.234
Penumbra volume, mean ± SD, mL	125.94±80.513
Mismatch volume, mL (IQR)	103.5 (46.5–148.5)
Mismatch ratio (IQR)	4.5 (0–7.025)
CBS (IQR)	7.5 [5–9]
Tan score (IQR)	2 [1–3]
24-h post-reperfusion infarct volume, mean ± SD, mL	60.71±77.729
Post reperfusion haemorrhage, n (%)	6 (17.6)

WUS, wake-up stroke; NCCT, non-contrast computed tomography; ASPECTS, Alberta stroke program early CT score; IQR, interquartile range; SD, standard deviation CBS, clot burden score.

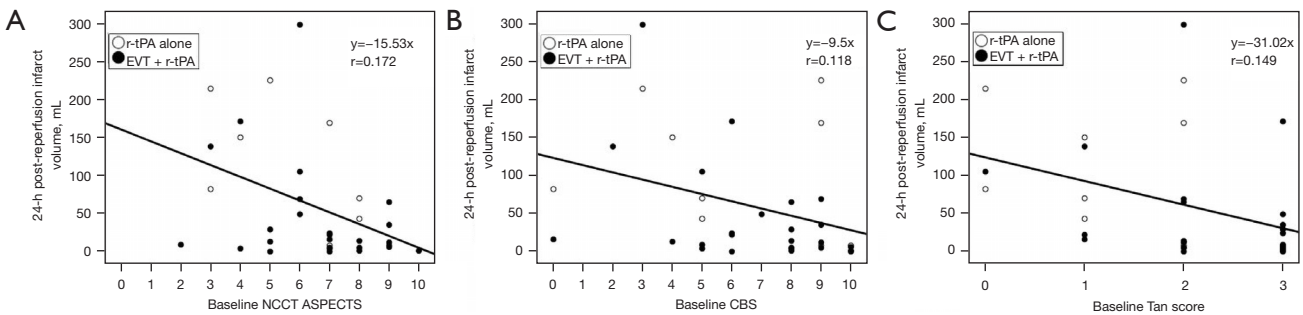

Figure 2 Scatter plots showing the relationship between baseline NCCT ASPECTS, baseline CBS, baseline Tan score to 24-h post-reperfusion infarct volume. Correlation of (A) baseline NCCT ASPECTS to 24-h post-reperfusion infarct volume; (B) baseline CBS to 24-h post-reperfusion infarct volume; (C) baseline Tan score to 24-h post-reperfusion infarct volume in all WUS patients, with regression line shown in black. r-tPA, recombinant tissue plasminogen activator; EVT, endovascular thrombectomy; NCCT, non-contrast CT; ASPECTS, alberta stroke program early CT score; CBS, clot burden score; WUS, wake-up stroke.

to –4.375; r=0.149; P=0.024). Between the baseline infarct with 24-h post-reperfusion infarct volume the slope of the regression line (*Figure 3A*) was 1.72 (95% CI: 0.797 to 2.638; r=0.311; P=0.001) and Bland-Altman plot (*Figure 3B*) shows 95% CI: 89.3 to –173.4 with the bias of –42.1 mL. Between the penumbra volume with 24-h post-reperfusion infarct volume the slope of the regression line (*Figure 3C*) was 0.33 (95% CI: 0.008 to 0.66; r=0.12; P=0.045) and Bland-Altman plot (*Figure 3D*) shows 95% CI: 242.7 to –112.1 with the bias is 65.2 mL.

Baseline infarct volume was similar in both reperfusion therapies groups (19 *vs.* 6 mL; P=0.273) (*Table 4*). WUS patients who received EVT were had significantly lower 24-h post-reperfusion infarct volume (82 *vs.* 14 mL; P=0.032), and had a significantly lower difference in infarct volume between 24-h post-reperfusion and baseline infarct

Table 3 Prediction of 24-h post-reperfusion infarct volume with baseline multimodal CT imaging characteristics of all included WUS patients

Baseline multimodal CT imaging	R-Squared	Coefficient	P value
NCCT			
NCCT ASPECTS	0.172	−0.415	0.015
CTP			
Infarct volume	0.311	0.558	0.001
Penumbra volume	0.12	0.346	0.045
CTA			
CBS	0.118	−0.343	0.047
Tan score	0.149	−0.387	0.024

WUS, wake-up stroke; NCCT, non-contrast computed tomography; ASPECTS, Alberta stroke program early CT score; CTP, CT perfusion; CTA, CT angiography; CBS, clot burden score.

volume (47 *vs.* 14 mL; P=0.04) (*Figure 4* and *Table 4*).

Discussion

The finding of this study is that baseline multimodal CT imaging characteristics such as NCCT ASPECTS, CBS, Tan score, infarct volume, and penumbra volume predicted 24-h post-reperfusion infarct volumes in WUS patients. In addition importantly, patients who underwent EVT had a significantly lower 24-h post-reperfusion infarct volume and a significantly lower difference in infarct volume between 24-h post-reperfusion and baseline infarct volume. And post EVT 6 WUS patients developed hemorrhage.

The degree of early ischemic change on NCCT in patients with AIS was assessed by ASPECTS (27). Several previous studies suggest that in AIS patients, NCCT ASPECTS can predict final infarct volume (33-35), which is consistent with our study. Higher baseline NCCT

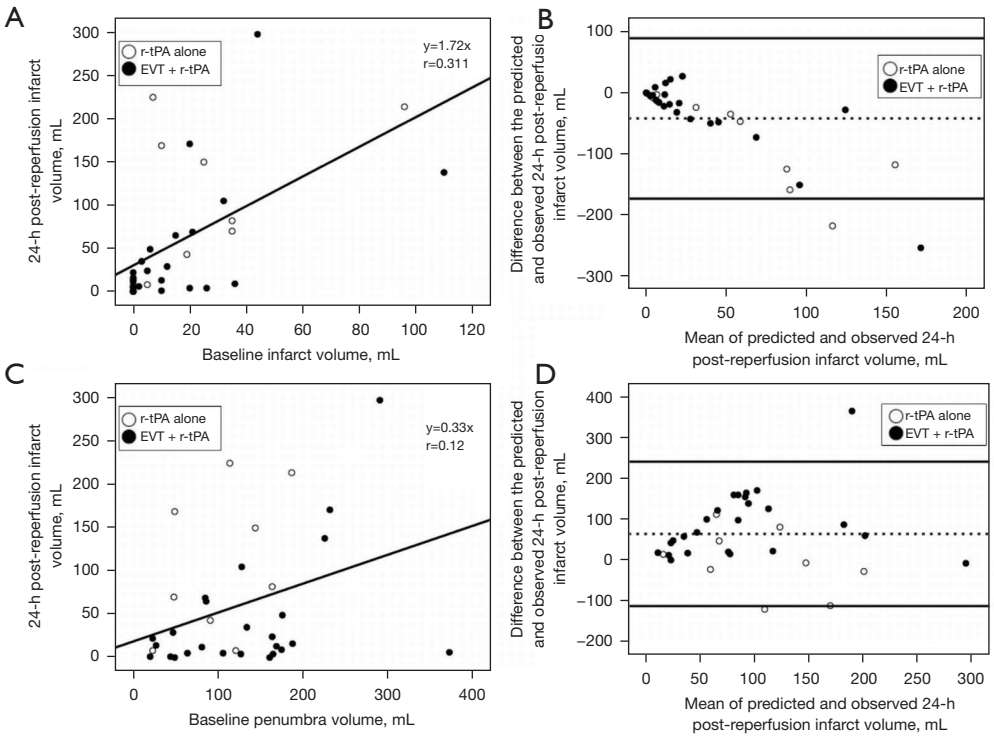

Figure 3 Scatter plots and Bland-Altman plots showing the relationship between baseline infarct volume, baseline penumbra volume to 24-h post-reperfusion infarct volume. The comparison of the baseline infarct volume with the 24-h post-reperfusion infarct volume shows in (A) scatter plot and (B) Bland–Altman plot. In Bland-Altman plot, 95% CI: 89.3 to −173.4 with the bias of −42.1 mL. The comparison of the baseline penumbra volume with the 24-h post-reperfusion infarct volume shows in (C) scatter plot and (D) Bland–Altman plot. In Bland-Altman plot, 95% CI: 242.7 to −112.1 with the bias is 65.2 mL. r-tPA, recombinant tissue plasminogen activator; EVT, endovascular thrombectomy.

Table 4 Analysis of infarct volume of all included WUS patients stratified by treatment module

Variables	r-tPA alone (n=9)	EVT with r-tPA (n=25)	P value
Baseline infarct volume, mL (IQR)	19 (6.0–35.0)	6 (0–20.5)	0.273
24-h post-reperfusion infarct volume, mL (IQR)	82 (25.5–191.5)	14 (4.5–57.0)	0.032
Difference of infarct volume, mL (IQR)	47 (16.0–142.0)	14 (0.5–37.5)	0.04

WUS, wake-up stroke; r-tPA, recombinant tissue plasminogen activator; EVT, endovascular thrombectomy; IQR, interquartile range.

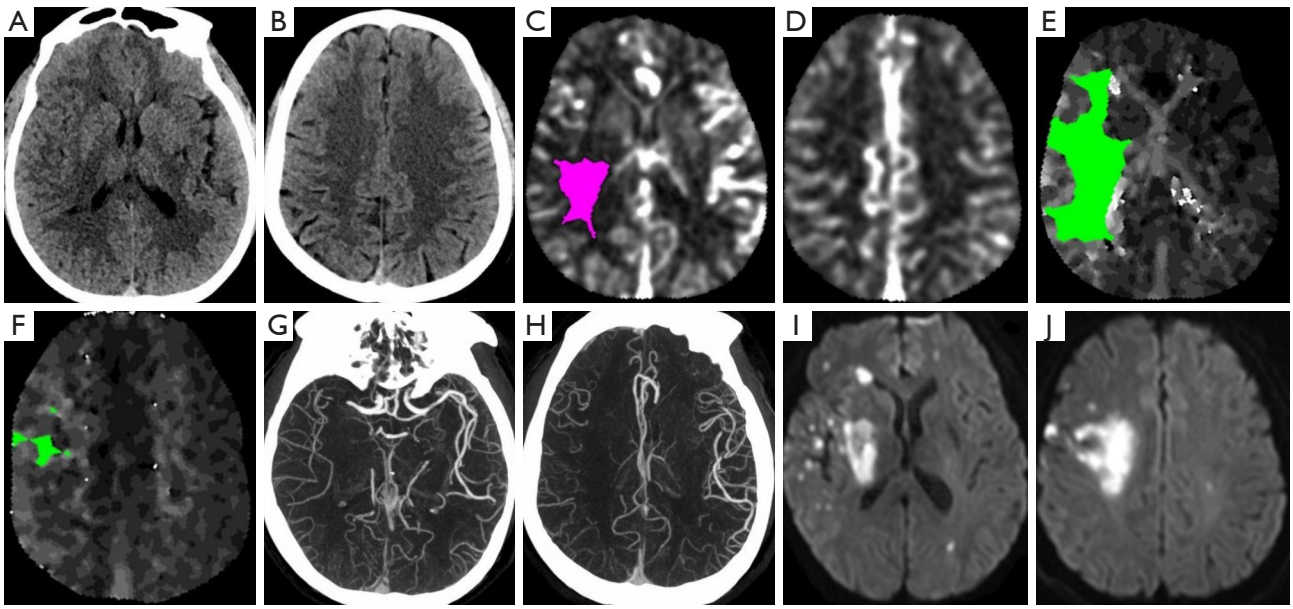

Figure 4 A 54-year-old male, WUS patient admitted with last seen well 6 h and 24 min and right MCA occlusion. Baseline (A,B) NCCT ASPECTS shows 9, (C,D) infarct volume 15 mL, (E,F) penumbra volume 86 mL, (G,H) good collateral (Tan score 2). Post EVT patient achieved good recanalization (TICI 3) with (I,J) 24-h post-reperfusion infarct volume is 65 mL. WUS, wake-up stroke; MCA, middle cerebral artery; NCCT, non-contrast CT; ASPECTS, alberta stroke program early CT score; EVT, endovascular thrombectomy; TICI, thrombolysis in cerebral infarction.

ASPECTS indicated smaller 24-h post-reperfusion infarct size in WUS patients. Vascular recanalization rates vary depending on thrombus location (36-38). Based on site and extent of intracranial occlusion, quantification of thrombus burden may therefore allow who might expect a differential treatment response (39). CTA is now commonly available in emergency departments and can rapidly, reliably and safely diagnose occlusion of major intracranial arteries and collateral (40). A study suggests that CBS on CTA can predict final infarct volume in AIS patients (41); our study correlates with this. Lower CBS designate a more extensive and extended thrombus burden in WUS patients, indicating a larger 24-h post-reperfusion infarct volume. Collateral circulation maintains penumbra perfusion, contributes to prolonged penumbral sustenance and is salvageable if timely recanalized (42). Good collateral circulation has been related with more significant perfusion-diffusion mismatches (43). The previous study shows that collateral correlates well with the final infarct volume in AIS (43-46), consistent with our study.

Some studies suggested that infarct volume and penumbra volume can predict infarct volume in AIS patients (18,19), which is consistent with our study. The baseline infarct volume often underestimated the 24-h post-reperfusion infarct volume in WUS patients. Possible explanations for this finding are: (I) between the imaging study at baseline and the time of reperfusion, infarct growth may have occurred; (II) to assess infarct on CTP a 30%

relative CBF threshold was used. When compared with DWI, study shows this conservative threshold slightly underestimate infarct volume (47); (III) few patients had oedema and hemorrhagic transformation after with reperfusion therapies, possibly from reperfusion injury. This likely contributed to the higher than predicted volume of the infarct observed 24-h after reperfusion therapy. This explain likely accounts for the significant differences between the predicted and actual infarct volume seen in this study's two outlier WUS patients. In this study, one case shows the baseline penumbra volume significantly overcalled the size of the 24-h post-reperfusion infarct volume. This case had good collaterals that may maintain the small infarct volume in a late time window. we assumed that the 24-h from reperfusion therapy to endpoint was too early to assess the final infarct volume in this patient. This finding of continued infarct growth up to 5 days from stroke onset has been previously described (48).

A recently published article demonstrated that in AIS patients, a larger 24-h post-reperfusion infarct size was an independent predictor of poor functional outcome (49). Our study showed that WUS patients who underwent EVT had lower 24-h post-reperfusion infarct volume. Thus, WUS patients who underwent EVT might achieve a good functional outcome. This opens up exciting pathways for future studies with prospective and larger sample sizes.

The study still has some limitations. (I) This study is retrospective and has a small sample size. Although this study enrolled a large number of patients at first, numerous heterogeneous cases were omitted after rigorous screening. Because small sample size further analyzing of data like 24-h post-reperfusion infarct volumes of patients under different treatment modalities over- or underestimated based on the regression line predictions was difficult. Future study with larger sample size would be sought (II) 24-h post-reperfusion is not likely to be the ideal time to assess infarct volume, as the ultimate infarct volume may be underestimated because the ischemic lesions are still growing or overestimated due to oedema and haemorrhage. The extended time window for measuring infarct volume in WUS patients are needed to be explored in future studies. (III) In this study linear model is used to predict 24-h post-reperfusion infract volume. In the future, proper validation is required using independent dataset.

Conclusions

Baseline multimodal CT imaging may predict infarct volume after reperfusion therapy in WUS patients. In addition, WUS patients who underwent EVT have a significantly lower infarct volume. These results support the evidence that multimodal CT imaging has the potential to perform an imperative role in both WUS patient selection and monitoring of the therapeutic response to interventions.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-614/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-614/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Our institutional review board reviewed and approved this study, and written informed consent was obtained from each patient.

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