A Study on Relationship of Hounsfield Units Value on Non-contrast Computer Tomography and Recanalization of Intravenous Thrombolysis

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Abstract: Objective: The objective of this study is to determine whether the administration of intravenous alteplase would be beneficial or futile to patients with acute ischemic stroke caused by large vessel occlusion (LVO) before endovascular treatment (EVT) and determine the relationship between Hounsfield units (HU) in non-contrast computed tomography (NCCT) and recanalization by alteplase.

Methods: We performed a retrospective analysis of patients with acute ischemic stroke caused by LVO who received intravenous thrombolysis (IVT) or followed by EVT at our center during November 2016 and October 2020. The clinical characteristics and imaging features of patients who achieved recanalization after IVT, and those who did not, were compared.

Results: Forty-three eligible patients were enrolled; 12 achieved recanalization by IVT. Baseline clinical characteristics did not differ between patients of the recanalization and non-recanalization groups. HU in the NCCT were estimated and statistically significant maximum and mean values of the ipsilateral middle cerebral artery (MCA) were found between the groups (P< 0.05). The results hint that patients in the non-recanalization group have a higher rHU and δHU value of the ipsilateral MCA compared with recanalization group (P< 0.05). With regards to the receiver operator characteristic (ROC) curve, we demonstrated that a high HU value of the ipsilateral MCA could be a predictor for non-recanalization by IVT.

Conclusion: Patients suffering LVO stroke are less likely to obtain recanalization by IVT with a high HU value of the ipsilateral MCA. It is feasible to screen patients with LVO using HU for directed EVT.

Keywords: Hounsfield units (HU), large vessel occlusion (LVO), non-contrast computed tomography (NCCT), recanalization, intravenous thrombolysis (IVT), endovascular treatment (EVT).

1. INTRODUCTION

Large Vessel Occlusion (LVO) is the most important pathogenic factor of acute ischemic stroke (AIS), accounting for approximately one third of all kinds of AIS. The first-line treatment status of Intravenous Thrombolysis (IVT) followed by Endovascular Treatment (EVT) is established by randomized clinical trials [1-5] and established by the American Heart Association/American Stroke Association (AHA/ASA) [6]. Cognizant of the safety, efficacy, and necessity of IVT before EVT, researchers have not surmised whether patients of AIS caused by LVO should be treated with bridging therapy (IVT followed by EVT) or EVT alone. IVT before EVT could reduce time to intervention and dissolve distal emboli as well as improve downstream reperfusion [7]. Recently, evidence that IVT is necessary before EVT for LVO patients was found [8]; but this is hindered by delayed initiation of femoral puncture, thrombus fragmentation, major bleeding, and increased financial burden [9-11]. The DITECT-MT trial demonstrated that the functional outcome of EVT alone was not inferior to IVT+EVT, despite a higher reperfusion rate before and post thrombectomy in the combination-therapy group [12]. Selecting patients who cannot recanalized by IVT to be treated with direct-EVT may reduce time to artery puncture and complications of hemorrhage, thereby improving the prognosis.
CT is the preferred imaging method for AIS recommended by the AHA/ASA guideline, as it can provide necessary information for prompt acute management decisions. Hounsfield unit (HU) is a parameter of CT reflecting the density of tissue and thrombi, with higher HU indicating higher density [13]. It has been speculated that HU is related to recanalization and outcome; however, opposite results were found from studies [14-18].

We found in our clinical experience that patients caused by LVO with low HU value may obtain recanalization by IVT alone and vice versa. We investigated the relationship between HU value and recanalization after IVT and discussed if HU value on non-contract CT (NCCT) could be a biomarker for selecting appropriate patients to be treated with direct-EVT.

2. MATERIALS AND METHODS

2.1. Patient Enrollment

We retrospectively reviewed all AIS patients with acute M1 segment of middle cerebral artery (MCA-M1) occlusion or concomitant occlusion of the MCA-M1 and internal carotid artery (ICA), as identified by MRI and digital subtraction angiography (DSA), computed tomographic angiography (CTA), or magnetic resonance angiography (MRA), who received IVT or IVT+EVT at the Affiliated Changsha Central Hospital, University of South China from November 2016 to October 2020. Detailed workflow for patient enrollment is shown in Fig. (1).

2.2. Acute Stroke Treatment and Imaging Protocols

For AIS treatment, IVT alone or in combination with EVT, was used to obtain fast revascularization within 4.5 hours or 6 hours, respectively. As patients with stroke symptoms were excluded from cerebral hemorrhage by CT, rtPA was given as soon as possible (10% injected intravenously and the remaining 90% continuously pumped for 1 hour). For EVT, the TREVO or Solitaire stent systems were used to retrieve the embolus.

CT examinations were performed using a commercially available multidetector raw scanner (GE Healthcare, USA). All included patients underwent NCCT scanning and CTA prior to IVT. Recanalization was estimated with DSA or CTA within 24 hours after treatment. For the measurement of HU value, the Information Technologies software of GE Medical Systems was used. Ten points in the route of the MCA in both ipsilateral and contralateral were randomly selected by two readers, who were blinded to the therapy and recanalization status and interobserver reliability was assessed. Furthermore, HU value of the brain tissue adjacent to the ipsilateral MCA was recorded for ten random points. Fig. (2) shows representative measuring sites of HU values. The maximum and mean values of the randomized ten points were calculated for statistical analysis. Recanalization was estimated by two independent neuroradiologists; when there was disagreement in assessment, a discussion was held to draw a conclusion.

![Flow chart of patients screening.](image-url)
Fig. (2). Typical example of NCCT and CTA imaging to show HU value measurement and occluded MCA. Patient 1 is representing who could not obtain reperfusion by IVT, and patient 2 representing who obtained reperfusion by IVT. (A and C) Representative NCCT imaging to exhibit sites of HU value measurement for ipsilateral MCA (red box), contralateral MCA (yellow box) and adjacent brain tissue of occluded MCA (yellow ovals); (B and D) Representative CTA imaging to show corresponding MCA occlusion. Abbreviations: L, left side; R, right side; MCA, middle cerebral artery (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2.3. Clinical Assessment

The National Institutes of Health Stroke Scale (NIHSS) was used to assess the neurologic deficits at baseline, immediately after treatment, and 24 hours after treatment: early neurological improvement was defined as a decrease of eight or more points or a score of 0 to 2 at 24 hours after intervention; [4]; early neurological deterioration was defined as an increase of four or more points at 24 hours after intervention. A favorable outcome was defined as mRS ≤2. Symptomatic intracranial hemorrhage (sICH) was defined as per the Heidelberg Bleeding Classification.

2.4. Patient and Public Involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research. The data of enrolled patients were extracted from available case files after approval from the Institutional Ethics Committee.

2.5. Statistical Analysis

Statistical analysis was performed with SPSS software (IBM SPSS Statistics for Windows, version 23.0). To determine the difference between patients who experienced recanalization and those who did not, we used Student's t-test, Mann-Whitney U test, chi-square test, or Fisher’s exact test. Normally distributed continuous variables, represented as mean ± SD, were analyzed using Student’s t-test; non-normally distributed continuous variables were represented as medians (interquartile range [IQR]) and analyzed using the Mann-Whitney U test. Ordinal categorical variables were represented as medians (IQR) and analyzed using the Mann-Whitney U test. Unordered categorical variables were represented as numbers (percentages) and chi-square test or Fisher’s exact test was used for analysis.

To explore the predictive accuracy of HU value on the ipsilateral MCA, the difference (δ) of HU value on ipsilateral MCA to contralateral MCA or adjacent brain tissue, and the ratio (r) of HU value on ipsilateral MCA to contralateral MCA or to adjacent brain tissue to differentiate patients who could not obtain recanalization from patients who obtained recanalization from rtPA, receiver operator characteristic (ROC) curves and the area under curve (AUC) was calculated. The max Youden Index was used to decide the cutoff points and corresponding sensitivities and specificities. Statistical significance was defined as P < 0.05 for all tests.

3. RESULTS

3.1. Demographic Data

A total of 43 patients were recruited in this study, with a median age of 64 (range 18-83), among which males accounted for approximately 53.5%. Successful recanalization was obtained by IVT alone in 12 patients, and 25 patients achieved successful reperfusion with the IVT in combina-
Table 1. Baseline characteristics of the 43 enrolled patients.

| Characteristics | Value |
|-----------------|-------|
| Age (years)     | 64 (60, 70) |
| Male            | 23 (53.5%) |
| Right side occlusion | 16 (37.2%) |
| TOAST           | -     |
| LAA             | 17 (39.5%) |
| CE              | 23 (53.5%) |
| SAO             | 0 (0%)  |
| ODC             | 1 (2.3%) |
| UND             | 2 (4.7) |
| Time from onset to CT scan (min) | 82.9 (59.1, 106) |
| Time from onset to rt-PA treatment (min) | 115 (80.0, 137) |
| Baseline NIHSS  | 17.0 (13.0, 22.0) |
| Recanalization  | -     |
| By IVT alone    | 12 (27.9%) |
| By IVT+EVT      | 25 (58.1%) |
| Max HU of ipsilateral MCA | 51.0±7.71 |
| Mean HU of ipsilateral MCA | 44.5±7.42 |
| Max HU of contralateral MCA | 41.9±4.42 |
| Mean HU of contralateral MCA | 35.3±3.60 |
| Max HU of adjacent brain tissue | 41.0±4.21 |
| Mean HU of adjacent brain tissue | 34.4±3.54 |
| δMax HU(iMCA-cMCA) | 9.00±7.63 |
| δMean HU(iMCA-cMCA) | 9.09±6.52 |
| δMax HU(iMCA-aBT) | 10.0±8.14 |
| δMean HU(iMCA-aBT) | 9.92±7.15 |
| rMax HU(iMCA-cMCA) | 1.22±0.191 |
| rMean HU(iMCA-cMCA) | 1.26±0.192 |
| rMax HU(iMCA-aBT) | 1.26±0.215 |
| rMean HU(iMCA-aBT) | 1.29±0.218 |
| Early neurological improvement | 9 (20.9%) |
| Early neurological deterioration | 7 (16.3%) |
| Favorable outcome | 20 (46.5%) |
| sICH            | 2 (4.65%) |
| Mortality       | 7 (16.3%) |

Abbreviations: LAA, Large Artery Atherosclerosis; CE, Cardiogenic Embolism; SAO, Small-Artery Occlusion; ODC, Stroke Of Other Determined Cause; UND, Stroke Of Undetermined Cause; NIHSS, National Institutes of Health Stroke Scale; IVT, Intravenous Thrombolysis; EVT, Endovascular Treatment; HU, Hounsfield Units; MCA, Middle Cerebral Artery; δMax HU(iMCA-cMCA), Difference of Max HU Value of Ipsilateral MCA to Max HU Value of Contralateral MCA; δMean HU(iMCA-cMCA), Difference of Mean HU Value of Ipsilateral MCA to Mean HU Value of Contralateral MCA; δMax HU(iMCA-aBT), Difference of Max HU Value of Ipsilateral MCA to Max HU Value of Adjacent Brain Tissue; δMean HU(iMCA-aBT), Difference of Mean HU Value of Ipsilateral MCA to Mean HU Value of Adjacent Brain Tissue; rMax HU(iMCA-cMCA), Ratio of Max HU Value of Ipsilateral MCA to Max HU Value of Contralateral MCA; rMean HU(iMCA-cMCA), Ratio of Mean HU Value of Ipsilateral MCA to Mean HU Value of Contralateral MCA; rMax HU(iMCA-aBT), Ratio of Max HU Value of Ipsilateral MCA to Max HU Value Of Adjacent Brain Tissue; rMean HU(iMCA-aBT), Ratio of Mean HU Value of Ipsilateral MCA to Mean HU Value of Adjacent Brain Tissue; Sich, Symptomatic Intracranial Hemorrhage.

To determine the probable factors which may affect recanalization, we compared age, gender, lesion side, concomitant occlusion, baseline NIHSS score, and time from onset to rt-PA intervention between patients with or without recanalization after IVT treatment. Early neurological improvement, early neurological deterioration, sICH, as well as functional outcome at the end of the 3rd month after AIS were also estimated between the two groups. The results showed that patients who obtained recanalization through IVT were more likely to reach early neurological improvement and favorable functional prognosis three months post-stroke; however, no statistical significance of sICH and early neurological deterioration was found between the two groups. These results may have been affected by the higher rate of failure of revascularization in the non-recanalization group. To eliminate this influence, we excluded patients who failed to obtain eventual recanalization and found that early neurological improvement and favorable outcomes were significantly higher in patients recanalized by IVT than those recanalized by IVT+EVT; whereas patients in the group recanalized by IVT+EVT appeared to have a higher rate of early neurological deterioration. No significant difference was detected between the two groups in terms of sICH and mortality. Detailed information is displayed in Table 2.

3.2. Clinical Characteristics

In Table 3, we summarized clinical characteristics of the patients with or without recanalization after IVT treatment. Among the 43 enrolled patients, 12 patients achieved successful revascularization with IVT treatment alone; 31 patients did not achieve recanalization through IVT, and subsequently received EVT.

3.3. Hounsfield Unit and Recanalization

Good interrater reliability was shown among two independent readers for maximum HU_{iMCA} (intraclass correlation coefficient (ICC) = 0.809), mean HU_{iMCA} (ICC = 0.812), maximum HU_{cMCA} (ICC = 0.941), mean HU_{cMCA} (ICC = 0.898), maximum HU_{aBT} (ICC = 0.819), and mean HU_{aBT} (ICC = 0.770). To explore the value of HU on NCCT in screening appropriate patients for bridging therapy or direct EVT, we analyzed absolute and relative values of HU, as presented in Table 4. Patients who achieved recanalization from IVT alone had a lower maximum and mean HU value of ipsilateral MCA, with statistical significance; while neither the absolute HU value on contralateral MCA nor the absolute HU value on the adjacent brain tissue showed a diff-
Table 2. Comparison of clinical outcome among patients recanalized by IVT or IVT+EVT.

| Outcome                          | Recanalized by IVT (n=12) | Recanalized by IVT+EVT (n=25) | P value  |
|----------------------------------|---------------------------|-------------------------------|---------|
| Early neurological improvement   | 8 (66.7%)                 | 1 (4.0%)                      | 0.000** |
| Early neurological deterioration | 0 (0.0%)                  | 7 (28.0%)                     | 0.045*  |
| sICH                             | 0 (0.0%)                  | 2 (8%)                        | 1.00    |
| Favorable outcome                | 11 (91.7%)                | 8 (32%)                       | 0.001** |
| Mortality                        | 0 (0.0%)                  | 5 (20%)                       | 0.152   |

Abbreviations: IVT, Intravenous Thrombolysis; EVT, Endovascular Treatment; sICH, Symptomatic Intracranial Hemorrhage. *P<0.05, **P<0.01.

Table 3. Comparison of clinical characteristics among patients with or without recanalization after IVT alone.

| Characteristic                        | Recanalization (n=12) | Non-recanalization (n=31) | P value  |
|---------------------------------------|-----------------------|---------------------------|---------|
| Age (years)                           | 62.0 (55.8, 63.5)     | 66.0 (60.0, 72.0)         | 0.073   |
| Male                                  | 4 (33.3%)             | 19 (61.3%)                | 0.099   |
| Right side occlusion                  | 4 (33.3%)             | 12 (38.7%)                | 1.00    |
| Concomitant occlusion                 | 1 (8.3%)              | 11 (35.5%)                | 0.130   |
| TOAST type                            | -                     | -                          | 0.318   |
| LAA                                   | 5 (41.7%)             | 18 (58.1%)                | -       |
| CE                                    | 5 (41.7%)             | 12 (38.7%)                | -       |
| ODC                                   | 1 (8.3%)              | 0 (0%)                     | -       |
| UND                                   | 1 (8.3%)              | 1 (3.2%)                  | -       |
| Time from onset to rt-PA              | 112 (88.3, 139)       | 115 (78.0, 137)           | 0.946   |
| Baseline NIHSS                        | 16.5 (9.25, 23.3)     | 17.0 (13.0, 22.0)         | 0.541   |
| Early neurological improvement        | 8 (66.7%)             | 1 (3.2%)                  | 0.000** |
| Early neurological deterioration      | 0 (0.0%)              | 7 (22.6%)                 | 0.075   |
| sICH                                  | 0 (0.0%)              | 2 (6.5%)                  | 0.373   |
| Favorable outcome                     | 11 (91.7%)            | 9 (29.0%)                 | 0.001** |
| Mortality                             | 0 (0.0%)              | 7 (22.6%)                 | 0.075   |

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; sICH, Symptomatic Intracranial Hemorrhage; LAA, Large Artery Atherosclerosis; CE, Cardioembolism; ODC, Stroke of Other Determined Cause; UND, Stroke of Undetermined Cause. **P<0.01.

Table 4. Comparison of imaging characteristics among patients with or without recanalization after IVT alone.

| Characteristic                        | Recanalization (n=12) | Non-recanalization (n=31) | P value  | ROC Curve |
|---------------------------------------|-----------------------|---------------------------|---------|-----------|
| Max HU of ipsilateral MCA             | 44.6±6.13             | 53.5±6.80                 | 0.000** | Cutoff Value: 49.5; AUC: 0.851; P: 0.000** |
| Mean HU of ipsilateral MCA            | 38.2±6.68             | 46.9±6.25                 | 0.000** | Cutoff Value: 42.3; AUC: 0.844; P: 0.001** |
| Max HU of contralateral MCA           | 42.3±6.26             | 41.7±3.60                 | 0.762   | Cutoff Value: 36.5; AUC: 0.488; P: 0.903 |
| Mean HU of contralateral MCA          | 34.8±5.13             | 35.5±2.89                 | 0.687   | Cutoff Value: 31.05; AUC: 0.574; P: 0.457 |
| Max HU of adjacent brain tissue       | 41.9±4.40             | 40.6±4.15                 | 0.387   | Cutoff Value: 34.5; AUC: 0.382; P: 0.234 |
| Mean HU of adjacent brain tissue      | 34.8±5.13             | 34.3±3.64                 | 0.810   | Cutoff Value: 29.3; AUC: 0.450; P: 0.616 |
| δMax HU (iMCA-cMCA)                   | 2.25±2.80             | 11.6±7.31                 | 0.000** | Cutoff Value: 7.5; AUC: 0.870; P: 0.000** |
| δMean HU (iMCA-cMCA)                  | 3.42±4.22             | 11.3±5.94                 | 0.000** | Cutoff Value: 9.20; AUC: 0.849; P: 0.000** |
| δMax HU (iMCA-aBT)                    | 2.67±7.66             | 12.9±6.76                 | 0.000** | Cutoff Value: 9.50; AUC: 0.858; P: 0.000** |
| δMean HU (iMCA-aBT)                   | 3.64±6.02             | 12.3±6.04                 | 0.000** | Cutoff Value: 9.45; AUC: 0.839; P: 0.001** |
| rMax HU (iMCA/cMCA)                   | 1.06±0.072            | 1.29±0.184                | 0.000** | Cutoff Value: 1.20; AUC: 0.860; P: 0.000** |
| rMean HU (iMCA/cMCA)                  | 1.10±0.137            | 1.32±0.173                | 0.000** | Cutoff Value: 1.15; AUC: 0.853; P: 0.000** |
| rMax HU (iMCA/aBT)                    | 1.07±0.173            | 1.33±0.187                | 0.000** | Cutoff Value: 1.27; AUC: 0.847; P: 0.000** |
| rMean HU (iMCA/aBT)                   | 1.11±0.181            | 1.37±0.188                | 0.000** | Cutoff Value: 1.27; AUC: 0.833; P: 0.001** |

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; IVT, Intravenous Thrombolysis; EVT, Endovascular Treatment; HU, Hounsfield Units; MCA, Middle Cerebral Artery; δMax HU(iMCA-cMCA), Difference of Max HU Value of Ipsilateral MCA To Max HU Value of Contralateral MCA; δMean HU(iMCA-cMCA), Difference Of Mean HU Value Of Ipsilateral MCA To Mean HU Value of Contralateral MCA; δMax HU(iMCA-aBT), difference of max HU value of ipsilateral MCA to max HU value of adjacent brain tissue; δMean HU(iMCA-aBT), difference of mean HU value of Ipsilateral MCA to mean HU value of adjacent brain tissue; rMax HU(iMCA/cMCA), Ratio of Max HU Value of Ipsilateral MCA To Max HU Value of Contralateral MCA; rMean HU(iMCA/cMCA), Ratio of Mean HU Value of Ipsilateral MCA To Mean HU Value of Contralateral MCA; rMax HU(iMCA/aBT), Ratio Of Max HU Value Of Ipsilateral MCA To Max HU Value of Adjacent Brain Tissue; rMean HU(iMCA/aBT), Ratio of Mean HU value of ipsilateral MCA to mean HU value of adjacent brain tissue; sICH, Symptomatic Intracranial Hemorrhage; AUC, Areas Under Curve. *P<0.05, **P<0.01.
dference between patients with or without recanalization after IVT alone. When the difference of maximum and mean HU values of ipsilateral MCA and adjacent brain tissue, defined as δMax HU\textsubscript{(iMCA-aBT)} and δMean HU\textsubscript{(iMCA-aBT)} respectively, was taken into account, we found a significant statistical difference between the two groups. Similarly, statistically significant differences were detected between patients with or without recanalization for ratio of maximum and mean HU values of ipsilateral MCA and adjacent brain tissue, defined as rMax HU\textsubscript{(iMCA/aBT)} and rMean HU\textsubscript{(iMCA/aBT)}, respectively. We also estimated the difference and ratio of ipsilateral to contralateral MCA HU values and recanalization after IVT. The results showed that the difference and ratio of HU values of ipsilateral to contralateral MCA was significantly higher in patients of the non-recanalization group than those of the recanalization group. Detailed information is displayed in Table 4.

Subsequently, we calculated the cutoff value of the maximum and mean values of ipsilateral MCA HU value with the best predictive capacity for non-recanalization by rtPA. The results showed that maximum HU value of ipsilateral MCA >49.5 could predict non-recanalization by rtPA, with the AUC, sensitivity, and specificity of 0.851, 74.2%, and 91.7%, respectively (Table 4). Similarly, the optimal cutoff of mean HU value of ipsilateral MCA was set as >42.3, with the AUC, sensitivity, and specificity of 0.844, 80.6%, and 83.3%, respectively. We also estimated the cutoff difference (δ) of maximum and mean HU values as ipsilateral MCA to contralateral MCA and to adjacent brain tissue, and found cutoff values of δMax HU\textsubscript{(iMCA-cMCA)} >7.5, δMean HU\textsubscript{(iMCA-cMCA)} >9.50, and δMean HU\textsubscript{(iMCA-aBT)} >9.45, respectively. Then, we used the same analysis to calculate the cutoff of ratio of max and mean HU value as ipsilateral MCA to contralateral MCA and to adjacent brain tissue. The results of the analysis showed rMax HU\textsubscript{(iMCA/aMCA)} >1.20, rMean HU\textsubscript{(iMCA/aMCA)} >1.15, rMax HU\textsubscript{(iMCA-aBT)} >1.27, and rMean HU\textsubscript{(iMCA-aBT)} >1.27. All AUCs of the calculated absolute ipsilateral MCA HU values and relative HU values of ipsilateral MCA to contralateral MCA or to adjacent brain tissue, were higher than 0.7, of which δMax HU\textsubscript{(iMCA-cMCA)} was the largest (0.870). Detailed information is displayed in Table 4 and Fig. (3).

### 3.4. Subgroup Analysis of Hounsfield Unit

To estimate the impact of occlusion site on HU value, we compared the max and mean HU value of ipsilateral MCA between patients of ICA+MCA occlusion and MCA occlusion. As shown in Fig. (4), HU values of ICA+MCA occlusion group were significantly higher than that in the single MCA occlusion group. Since combination occlusion of ICA and MCA make a difference in HU value, we then conducted the subgroup analysis that only single MCA occlusion was enrolled, with a total number of 31 patients. Eleven of them obtained reperfusion by IVT treatment and 20 did not get reperfusion by IVT. As shown in Table 5, the max and mean HU value of ipsilateral MCA is higher in patients who could not receive reperfusion, the same as relative HU value when compared with contralateral MCA and adjacent brain tissue.

![Fig. (3). Receiver operator characteristic curves of absolute and relative HU values of ipsilateral MCA.](image)

Values used to predict non-recanalization by rtPA. (A) Absolute max and mean HU value of ipsilateral MCA; (B) Relative (difference [δ] and ratio) max and mean HU value of ipsilateral MCA to contralateral MCA; (C) Relative (difference [δ] and ratio) max and mean HU value of ipsilateral MCA to adjacent brain tissue (A higher resolution / colour version of this figure is available in the electronic copy of the article).

### Table 5. Comparison of imaging characteristics among patients of MCA occlusion with or without recanalization after IVT alone.

| Characteristic                  | Recanalization (n=11) | Non-recanalization (n=20) | P value |
|--------------------------------|-----------------------|---------------------------|---------|
| Max HU of ipsilateral MCA      | 43.6±5.20             | 51.8±6.48                 | 0.001** |
| Mean HU of ipsilateral MCA     | 37.1±5.75             | 45.3±6.10                 | 0.001** |
| Max HU of contralateral MCA    | 41.4±5.54             | 41.6±3.89                 | 0.913   |
| Mean HU of contralateral MCA   | 33.9±4.29             | 35.4±3.23                 | 0.303   |
| Max HU of adjacent brain tissue| 42.2±4.51             | 40.4±4.49                 | 0.287   |

(Table 5 contd...)
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| Characteristic                  | Recanalization (n=11) | Non-recanalization (n=20) | P value |
|--------------------------------|-----------------------|---------------------------|---------|
| Mean HU of adjacent brain tissue | 34.6±3.57             | 34.0±4.03                 | 0.673   |
| δMax HU (iMCA-cMCA)             | 2.18±2.93             | 10.2±7.73                 | 0.000** |
| δMean HU (iMCA-cMCA)            | 3.21±4.36             | 9.93±6.17                 | 0.003** |
| δMax HU (iMCA-aBT)              | 1.35±5.28             | 11.4±6.31                 | 0.000** |
| δMean HU (iMCA-aBT)             | 2.55±4.90             | 11.2±5.91                 | 0.000** |
| rMax HU (iMCA/aBT)              | 1.06±0.076            | 1.26±0.197                | 0.000** |
| rMean HU (iMCA/aBT)             | 1.10±0.144            | 1.29±0.186                | 0.007*  |
| rMax HU (iMCA/cMCA)             | 1.04±0.137            | 1.29±0.176                | 0.000** |
| rMean HU (iMCA/cMCA)            | 1.08±0.152            | 1.34±0.189                | 0.000** |

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; IVT, Intravenous Thrombolysis; EVT, Endovascular Treatment; HU, Hounsfield Units; MCA, Middle Cerebral Artery; δMax HU(MCA-cMCA), Difference of Max HU Value of Ipsilateral MCA to Max HU Value of Contralateral MCA; δMean HU(iMCA-cMCA), Difference of Mean HU Value of Ipsilateral MCA to Mean HU Value of Contralateral MCA; δMax HU(iMCA-aBT), Difference of Max HU Value of Ipsilateral MCA to Max HU Value of Adjacent Brain Tissue; δMean HU(iMCA-aBT), Difference of Mean HU Value of Ipsilateral MCA to Mean HU Value of Adjacent Brain Tissue; rMax HU(iMCA/aBT), Ratio of Max HU Value of Ipsilateral MCA to Max HU Value of Adjacent Brain Tissue; rMean HU(iMCA/aBT), Ratio of Mean HU Value of Ipsilateral MCA to Mean HU Value of Adjacent Brain Tissue; δMean HU (iMCA-cMCA), Difference of Mean HU Value of Ipsilateral MCA to Mean HU Value of Contralateral MCA; rMax HU(iMCA/cMCA), Ratio of Mean HU Value of Ipsilateral MCA to Mean HU Value of Contralateral MCA; rMean HU (iMCA/cMCA), Ratio of Max HU Value of Ipsilateral MCA to Max HU Value of Adjacent Brain Tissue; Sich, Symptomatic Intracranial Hemorrhage; AUC, Areas Under Curve. **P< 0.01.

4. DISCUSSION

We demonstrated that some patients with LVO could reach successful recanalization by treatment of IVT alone, and patients who achieved recanalization by IVT alone seem to have a lower HU value (both maximum and mean of the ten points recorded) compared with those who could not obtain recanalization by IVT alone. To eliminate the influence of examinations at different times for individuals, the HU value of contralateral MCA and adjacent brain tissue were used as internal references. The results showed that a higher difference (δ) and ratio of maximum and mean HU value of ipsilateral MCA to contralateral MCA, or to adjacent brain tissue, were detected in patients who did not achieve recanalization by IVT. Both absolute and relative (difference and ratio of ipsilateral to contralateral MCA or ipsilateral MCA to adjacent brain tissue) high HU values of ipsilateral MCA had a good ability to predict non-recanalization. In terms of clinical outcome, we found the rate of early neurological improvements and favorable functional outcomes was significantly higher in patients who attained recanalization by IVT alone, with the same risk of sICH.

4.1. Significance of Stratification in Patients with LVO

IVT is the most effective strategy for AIS, but it has limited effect on strokes caused by LVO, as published studies [1-5, 19-22]. Endovascular treatment has been confirmed effective for LVO stroke, while if LVO patients should receive endovascular treatment directly remained to be explored. Most recently, researchers of SKIP and DIREC-T-MT reported their studies which were aimed at comparing efficacy and safety of direct EVT or bridging therapy on patients with LVO, and results showed that direct EVT was noninferior to bridging therapy [12, 23]. We learned experience from studies of negative results [24-26] and positive results [1-5] from their opposite results on EVT for stroke patients with LVO. The latter obtained favorable outcome can be attributed to strict screening of patients with LVO and application of the new generation of thrombectomy equipment. From this point of view, the stratification of different patients may be one of the most important factors to implement an individualized treatment strategy. On the one hand, we should not treat all LVO patients with EVT directly as a considerable proportion of patients can get recanalization. According to the results of published multicenter randomized controlled trials, the recanalization rate of patients with LVO treated by IVT alone was between 7~37.3% [1-5, 12]. In our current study, 27.9% of patients who suffered LVO could obtain recanalization by IVT, and the rates of early neurological improvement and favorable outcome at 3rd month of these patients were significantly higher than those received bridging therapy. The possible reason is that recanalization by IVT shortened the time from symptom onset to reperfusion. If the patients who can be recanalized by IVT are treated with direct EVT, it will undoubtedly delay the reperfusion, and we all know that there is a definite correlation between delayed reperfusion and poor prognosis [27, 28]. In this respect, not all patients with LVO are suitable for EVT. On the other hand, IVT before EVT may increase the risk of cerebral hemorrhage and brain edema, for alteplase increase the level of MMP9, which leads to the destruction of blood-brain barrier [29, 30]. Since the overall results of the studies suggested that direct EVT is noninferior to bridging therapy, [12, 23] can the cancellation of invalid thrombolysis bring better results to patients due to the reduce the time to reperfusion and the incidence of complications? Therefore, we speculate that it is very important to distinguish the patients who can obtain recanalization from IVT. Treated patients who can be recanalized by IVT with alteplase and who cannot be recanalized by IVT with direct...
4.2. The Effect of HU value on the Stratification of Patients

Identification of thrombus components may be helpful in predicting the sensitivity of thrombus to intravenous thrombolysis, as preclinical research showed that platelet-rich thrombus is much more resistant to thrombolysis with rt-PA than an erythrocyte-rich clot. HU value is a parameter reflecting tissue density, which has a good value in differentiating hyperdense middle cerebral artery sign (HMCA$\text{S}$) in stroke patients from asymmetric hyperdensity unrelated to stroke [15, 31, 32]. Several studies reported the HU value has a good roll in reflecting the component of thrombus, with a higher HU value indicate “red clots”, namely a higher erythrocyte density; while a low HU value is associated with higher fibrin density, defined as “white clots” [33, 34]. Kim et al. reported that erythrocyte-rich clots increase HU value and are more susceptible to thrombolysis agents, while the platelet rich clots are on the contrary [16]. Besides, HU value may play a role in identifying the source of thrombus. Fibrin-rich and erythrocyte-rich clots were presumed to originate from cardiac sources, and clots with a predominant platelet composition were more likely to stem from larger arteries [35]. In contrast, other studies hold the opposite opinion that clots of large arteries derived were erythrocyte-rich and cardiac might have a higher component of fibrin [36, 37]. Two reasons were speculated to be potential causative factors for the conflicting results: only part of the clot were taken out for analysis by EVT, and using of IVT before EVT may have an impact on the composition of clots. In a different way, HU value was deemed to be not only related to proportion but also related to content and volume of erythrocyte [38]. As a consequence, the more distant the clot located, the smaller the diameter and the lower HU value. This idea is consistent with what Puig et al. showed [17]. And in our current study, combined occlusion of ICA and MCA had a significantly higher HU value than that of single occlusion of MCA, which also supports this view of point.

Sufficient contact with thrombus is necessary for alteplase to play its role. Therefore, thrombus with larger size and lower permeability seems to have less chance to be dissolved. HU value has been used to evaluate the permeability of thrombus, as the permeability was defined by D-value of HU value on CTA and NCCT. Our current results demonstrated that larger clots of concomitant occlusion of ICA and MCA had a higher HU value and worse IVT response than smaller clots of single MCA occlusion. This is consistent to the previous study which demonstrated that the more proximal and longer clots, the higher HU value [39]. As we all know, proximal occlusion showed a larger clot and suffered relative lower recanalization rate by rt-PA [40]. It can be inferred that the higher the HU value is, the more difficult it is to achieve recanalization through intravenous thrombolysis. Besides, researchers investigated relationship between HU value and recanalization. Previous studies deemed that HU value could be a useful tool to predicate the susceptibility of thrombus to reperfusion therapy [18]. It has been reported that an rHU $<1.382$ may predict non-recanalization after IVT [17], and a lower HU value seems to more resistant to pharmacological thrombolysis and mechanical thrombectomy [16, 41]. Whereas, an rHU value above 1.1 was reported to have a higher rate of unfavorable outcomes [14], which contradicts previous studies reporting that early successful recanalization is an important factor to improve prognosis [42-44]. In addition, relationship between HMCA$\text{S}$ and prognosis is controversial, with some studies reporting an unfavorable outcome for patients with HMCA$\text{S}$ [45-48], while others holding the opinion that HMCA$\text{S}$ is useless in predicting functional outcome [49-51]. HU value may be a promising indicator for revascularization, but the researchers have not been achieved a consistent conclusion. In the present study, we detected that a high HU value of ipsilateral MCA could be a predictor for non-recanalization. Probable reasons why our results are different from others may include following: firstly, patients of M2 or more distal occlusion were excluded from this study, while most of the conducted studies included patients of M2-MCA occlusion; secondly, rtPA is the only pharmacological thrombolysis drug used in our center, while other stroke centers may also use tPA or urokinase; thirdly, we calculated recanalization by IVT only, whereas other studies counted all recanalization including IVT, arterial thrombolysis, EVT, and bridging therapy; finally, difference of scanning devices and calculation methods may impact on the different results. Different from studies which focused on the issue that HU value may be a predictor for recanalization or functional outcome, we explored the question of whether if rtPA is futile to patients with a high HU value, IVT can be withheld. HU value is extremely easy to acquire, as a CT can be performed quickly in any hospital, without additional software for calculations. This additional advantage makes HU value a promising indicator. Due to the small sample size, however, the results are not enough to be generalized.

There are some limitations in our current study. Firstly, the retrospective study is prone to selection biases, and prospective, randomized controlled trials are expected to be conducted. Secondly, extrapolation of our results is restricted due to the very small sample size; but retrospective studies derived from real-life are more representative of current clinical practice. Clinical trials with larger number of patients are needed to generalize this result. Thirdly, NCCT was scanned with 5-mm slice thickness in our center, which may lead to some segments of the MCA not being displayed on coronal images. A thinner CT scan is expected to solve this problem. Fourthly, the calcified plaque located on the MCA may exert an impact on HU value, and we have recorded 10 randomized points to reduce this influence. Lastly, the treatment procedure was performed according to the guidelines at the time, and no patients eligible for IVT received direct EVT, leading to a lack of straightforward comparison between direct EVT and bridging therapy. Randomized clinical trials are needed to compare the safety and efficacy of direct EVT and bridging therapy in AIS patients caused by LVO with high MCA HU values.
CONCLUSION

In conclusion, patients suffering LVO stroke are less likely to obtain recanalization by IVT with a high HU value of the ipsilateral MCA. It may be feasible to screen patients with LVO and a high HU value for direct EVT. Further prospective clinical trials are warranted to verify this speculation.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This retrospective study was approved by the ethics committee of the Affiliated Changsha Central Hospital, University of South China, China.

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. All the humans used were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ ecodes/node/3931).

CONSENT FOR PUBLICATION

Not applicable.

STANDARD OF REPORTING

STROBE guidelines were followed in this study.

AVAILABILITY OF DATA AND MATERIAL

The data that support the findings of this study are available from the corresponding author, [ZS] upon reasonable request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial, or otherwise.

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