# MECHANISMS, MEASUREMENT, AND MANAGEMENT OF VASOGENIC EDEMA AFTER STROKE

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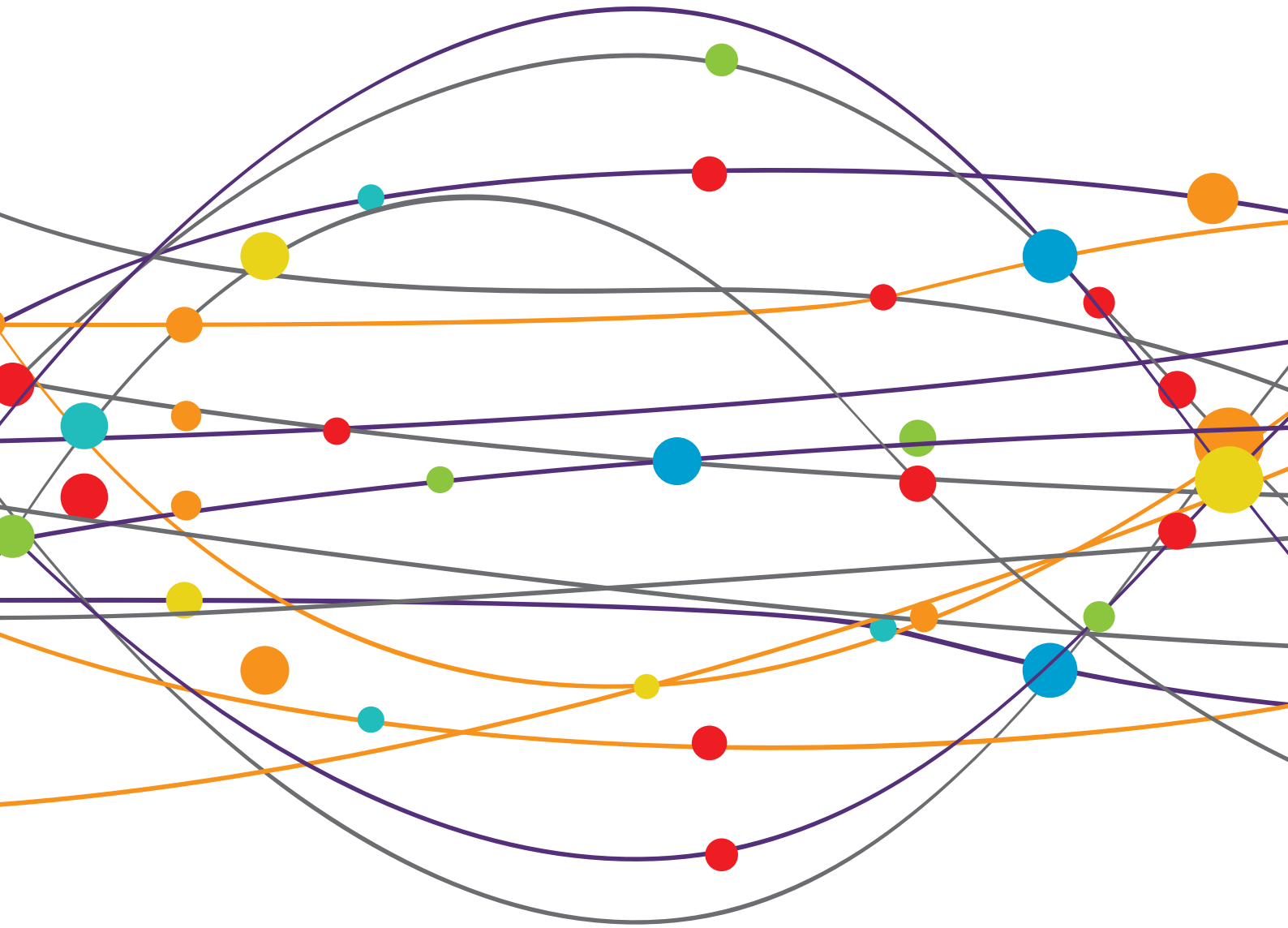

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# MECHANISMS, MEASUREMENT, AND MANAGEMENT OF VASOGENIC EDEMA AFTER STROKE

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# Editorial: Mechanisms, Measurement, and Management of Vasogenic Edema After Stroke

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**Keywords: stroke, edema, ischemia, imaging, infarction**

**Editorial on the Research Topic**

**Mechanisms, Measurement, and Management of Vasogenic Edema After Stroke**

## INTRODUCTION

Cerebral tissue edema is a pathophysiological hallmark of acute ischemic injury. Cerebral ischemia induced by critical brain perfusion results in disturbed water homeostasis, and subsequently a net uptake of water and cations into the ischemic tissue. In large ischemic lesions, as a severe complication, progressive water uptake may lead to severe space-occupying edema within the first days after stroke onset with mortality up to 80% (1, 2). Therefore, the identification and validation of reliable neuroimaging biomarkers for developing brain edema remains an elementary challenge of stroke imaging despite recent advances in artificial intelligence-based automated imaging tools. Furthermore, it has recently been observed that treatment strategies in ischemic stroke directly affect the formation of vasogenic edema following stroke (3–5). Hence, ischemic vasogenic edema may be a therapeutic target for both endovascular treatment, as well as novel adjuvant neuroprotective drugs (6). The aim of this Research Topic was to investigate neuroimaging biomarkers of ischemic vasogenic edema in acute stroke for imaging triage, measurement of treatment effects, and prediction of functional outcome.

## MECHANISMS OF VASOGENIC EDEMA AFTER STROKE

The identification of variables associated with the progression of ischemic edema is a fundamental challenge in the asssessment of acute ischemic stroke patients on admission, particularly considering modifiable variables that could be used to alter the progression of infarction. Nawabi et al. hypothesized that baseline serum glucose, which is known to be associated with functional outcome and response to endovascular treatment, interacts with the effect of tissue water uptake on the occurrence of intracerebral hemorrhage (ICH), a major complication after reperfusion therapy. It was observed that a higher degree of early tissue water uptake and high admission serum glucose were both independent predictors of ICH. Although a clear causal relationship remains speculative, stricter glucose control, and monitoring could be tested to reduce the risk of ICH in patients undergoing thrombectomy.

In the further course of ischemic brain infarct, vasogenic edema progresses and constitutes up to 35% of the total infarct lesion volume. Konduri et al. sought to elucidate the role of edema in subacute lesion progression and its influence on unfavorable functional outcome by quantifying

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net water uptake including patients from the MR CLEAN trial. It was observed that edema volume ususally increases in the period between 1 day and 1 week after acute ischemic stroke, depending on the degree of recanalization, and was significantly associated with functional outcome.

So far, limited data exist regarding the hemispheric differences in the incidence of stroke-related complications and outcomes of patients with extensive baseline stroke. Li et al. assessed the hemispheric differences with characteristics, complications, and outcomes of patients suffering from large hemisphere infarctions (LHI). Li et al. observed that right-sided patients with LHI had higher frequency of atrial fibrillation and cardio-embolism than the left-sided patients, whereas stroke lateralization was not an independent predictor of mortality and unfavorable outcome.

## MEASUREMENT OF VASOGENIC EDEMA AFTER STROKE

Malignant cerebral edema (MCE) following ischemic stroke regularly results in very poor outcomes. Hence, the early prediction of MCE might help to identify patients that could benefit from decompressive surgery. Quantitative net water uptake (NWU) has been described as a predictor of MCE; however, the utilization of CT perfusion and lesion segmentation is currently necessary for NWU assessment. Fu et al. proposed a new Image Patch-based Net Water Uptake (IP-NWU) procedure that only uses non-enhanced admission CT and does not need lesion segmentation. In summary, IP-NWU showed a high diagnostic accuracy to predict MCE, with an AUC of 0.86. By combining IP-NWU with imaging features through a random forest classifier, the radiomics model achieved even an AUC of 0.96. Xu et al. aimed to investigate whether NWU calculated in standardized and blindly outlined regions of the middle cerebral artery territory can predict the development of MCE, aiming to further standardize and simplify the procedure of NWU quantification. Xu et al. concluded that NWU calculated in standardized and blindly outlined regions of the middle cerebral artery territory was a good predictor for the development of MCE (AUC: 0.73).

Steffen et al. performed a pilot study to investigate the potential value of dual-energy dual-layer CT after mechanical thrombectomy (MT) for the improved assessment of ischemic edema, as it is known that contrast staining after MT might directly affect the measurement of NWU (7). NWU was measured in conventional polychromatic CT images and virtual non-contrast images in a blinded fashion. It was observed that NWU may be quantified precisely on conventional CT images, as the underestimation of ischemic edema due to contrast staining was low. Nonetheless, a relevant proportion of patients after MT (2 out of 10 patients) might show significant contrast staining resulting in edema underestimation.

The measurement of quantitative NWU is not yet established in acute stroke triage. Bechstein et al. propose a simple imaging score to be applied on baseline non-enhanced CT images (i.e., "NEMMI score"). It was hypothesized that this score, consisting of measurements of visually evident ischemic changes (sum of the maximum diameter anterior-poster + mediolateral of the hypoattenuated lesion in baseline-CT multiplied by a hypoattenuation factor) on non-enhanced CT predicts malignant middle cerebral artery infarctions with a high diagnostic power. In conclusion, the authors observed that the NEMMI score might serve as a quick and simple rating tool of early ischemic changes on CT and could serve as a surrogate marker for developing malignant edema. Its diagnostic accuracy was similar to CTP and clinical parameters.

Finally, the quantification of early edematous water uptake might have particular importance in the assessment of patients with extensive baseline infarction (i.e., low ASPECTS). The rating of ASPECTS is based on the presence of hypoattenuation of the ischemic brain tissue, which is directly related to early infarct, and the degree of relative hypoattenuation can be used to quantify ischemic edema on CT. The purpose of the pilot study of Broocks et al. was to evaluate how early tissue water uptake in acute ischemic brain might determine lesion fate and functional outcome in low ASPECTS patients undergoing MT. In this single center analysis of 155 low ASPECTS patients, NWU showed to be an independent predictor of outcome. While low NWU was a beneficial constellation regarding the effect of recanalization on outcome, high NWU was associated with futile recanalization. Further research is necessary to elucidate the value of quantitative NWU in the assessment of low ASPECTS patients.

## MANAGEMENT OF VASOGENIC EDEMA AFTER STROKE

Currently it is tested, whether Glibenclamide, a sulfonylurea, improves outcome in large hemispheric stroke and reduces formation of ischemic edema (6). Zhao et al. aim to explore the efficacy of small doses of oral glibenclamide in perihematomal edema (PHE) and the prognosis of patients with ICH in a clinical trial (GATE-ICH, NCT03741530). The study assesses the effects of small doses of oral glibenclamide in reducing the PHE after ICH and improving the 90-day prognosis of patients. Similarly, Jingjing et al. assessed whether sulfonylureas are associated with lower PHE and improved clinical outcomes in diabetic patients who have acute basal ganglia hemorrhage. In this case-control study, Jingjing et al. concluded that pretreatment with sulfonylureas were associated with lower PHE and relative PHE on admission. No significant effect was found on the clinical outcomes when the patients were discharged. Still, the authors see a need for further studies to assess the potential clinical benefit using sulfonylureas for ICH patients.

## DISCUSSION AND FUTURE CHALLENGES

Neuroimaging biomarkers of ischemic edema in acute stroke are highly relevant for imaging triage of stroke patients, to measure and compare treatment effects, and to predict functional outcome. First, it is important to realize that the term "edema" is regularly connected with different meanings, such as "swelling" (i.e., expansion of an infarct lesion with adjacent anatomy shift), or "net uptake of water" into the ischemic tissue which is evident

by progressive hypoattenuation even below visually evident brain swelling. The precise quantification of early edema remains an elementary challenge, and NWU may particularly serve as a tool to select patients for treatment. Current trials may have missed this opportunity.

For instance, it is yet uncertain how to select patients with a low ASPECTS for endovascular treatment (8, 9). The currently active low ASPECTS trials apply different inclusion criteria based on ischemic core volume or ASPECTS. However, the degree of hypoattenuation, which directly reflects net uptake of water, is currently not considered as imaging biomarker in stroke triage. As described in the above-mentioned pilot study, the degree of water uptake as quantified on baseline CT might serve as a predictor of outcome, and could be tested as a tool to select low ASPECTS patients for thrombectomy (10). A further application of edema imaging is to guide adjuvant treatment. The CHARM trial (NCT02864953) is a phase 3 study to evaluate the efficacy and safety of intravenous glibenclamide for severe cerebral edema. However, this study only includes patients with visually evident and apparent large infarct lesions, in particular patients after thrombectomy (likely the majority or large minority of patients) when inclusion criteria are met on follow-up MRI DWI scans. Alternatively, NWU on baseline CT could be used to select patients for glibenclamide administration early prior to visually apparent brain swelling, before, or during thrombectomy to mediate the detrimental effect of net water uptake at an early ischemic lesion stage, which may progress to high levels quickly often resulting in malignant edema and futile recanalization (3, 11, 12).

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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# Image Patch-Based Net Water Uptake and Radiomics Models Predict Malignant Cerebral Edema After Ischemic Stroke

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Malignant cerebral edema (MCE) after an ischemic stroke results in a poor outcome or death. Early prediction of MCE helps to identify subjects that could benefit from a surgical decompressive craniectomy. Net water uptake (NWU) in an ischemic lesion is a predictor of MCE; however, CT perfusion and lesion segmentation are required. This paper proposes a new Image Patch-based Net Water Uptake (IP-NWU) procedure that only uses non-enhanced admission CT and does not need lesion segmentation. IP-NWU is calculated by comparing the density of ischemic and contralateral normal patches selected from the middle cerebral artery (MCA) area using standard reference images. We also compared IP-NWU with the Segmented Region-based NWU (SR-NWU) procedure in which segmented ischemic regions from follow-up CT images are overlaid onto admission images. Furthermore, IP-NWU and its combination with imaging features are used to construct predictive models of MCE with a radiomics approach. In total, 116 patients with an MCA infarction (39 with MCE and 77 without MCE) were included in the study. IP-NWU was significantly higher for patients with MCE than those without MCE ($p < 0.05$). IP-NWU can predict MCE with an AUC of 0.86. There was no significant difference between IP-NWU and SR-NWU, nor between their predictive efficacy for MCE. The inter-reader and interoperation agreement of IP-NWU was exceptional according to the Intraclass Correlation Coefficient (ICC) analysis (inter-reader: ICC = 0.92; interoperation: ICC = 0.95). By combining IP-NWU with imaging features through a random forest classifier, the radiomics model achieved the highest AUC (0.96). In summary, IP-NWU and radiomics models that combine IP-NWU with imaging features can precisely predict MCE using only admission non-enhanced CT images scanned within 24 h from onset.

**Keywords: malignant cerebral edema, predictive model, radiomics, CT image, ischemic stroke, net water uptake**

## INTRODUCTION

Stroke is the leading cause of death and disability, resulting in 5.9 million deaths and 102 million disability-adjusted life-years worldwide (1). Ischemic stroke accounts for about 85% of the total incidence (2). A focal occlusion at the middle cerebral artery (MCA) leads to large hemispheric infarctions in some patients since the MCA supplies a large amount of blood to the brain.

Progressive cerebral edema usually results in a space-occupying infarct. The edema increases both brain volume and intracranial pressure. In the first 1–3 days after the onset of stroke, an abrupt neurological decline associated with displacement of midline brain structures may occur in ∼10% of the patients with ischemic stroke of the MCA (3–5). These tissue shifts and subsequent brain herniation make the mortality rate increase to nearly 80% and thus are termed malignant cerebral edema (MCE) or malignant MCA infarction (6, 7). MCA can be relieved by decompressive craniectomy performed within 48 h of stroke onset or before herniation (3, 8).

Early and precise prediction of MCE can help identify the patients who could potentially benefit from a surgical decompressive craniectomy. Moreover, it can also help clinicians prepare for possible deterioration and communicate with patients and their family members about the goals of care (5). Compared with MRI, CT is the most favorable imaging modality for the prediction of MCE due to its fast acquisition and widespread availability. For example, Minnerup et al. (6) proposed the use of CT-based cerebrospinal fluid (CSF) volume as a predictor of MCE. The ischemic lesion volume must be measured manually from the admission perfusion CT images (cerebral blood volume, CBV). The clot burden score and collateral score measured from CT angiography have also been considered as predictors of MCE (9). Ong et al. developed the Enhanced Detection of Edema in Malignant Anterior Circulation Stroke (EDEMA) to predict the risk of lethal malignant edema; it includes two CT imaging variables at 24 h after the midline shift and basal cistern effacement (10). The EDEMA score showed a higher positive predictive value (93%) than the baseline image markers, such as the Alberta Stroke Program Early CT score (ASPECTS) or hyperdense vessel sign. Cheng et al. added the National Institute of Health Stroke Score (NIHSS) into EDEMA and validated it using a dataset of Chinese patients (11). Two recent meta-analysis studies summarized additional potential predictors (12, 13).

Net water uptake (NWU) measured by non-enhanced CT is useful for predicting malignant infarctions. A CBV map driven from CT perfusion (CTP) can be used to precisely locate the early ischemic infarct core and a non-enhanced CT is applied to quantitatively measure density changes. The NWU is calculated using the formula $1\text{-}D_{Ischemic}/D_{Normal}$, where $D_{Ischemic}$ (HU) is the density of the ischemic core with hypoattenuation and $D_{Normal}$ is the density of the area of the contralateral normal tissue (14–16).

Radiomics aims to extract high-dimensional and quantitative features from medical images that can be used to build predictive models with machine learning methods to support clinical decisions (17, 18). Radiomics has played an important role in the study of many diseases such as cancers (19, 20). For stroke management, radiomics have been used to predict recanalization in ischemic stroke and hematoma expansion (21, 22). However, no study on predicting MCE by radiomics has been reported.

Regarding NWU and the prediction of MCE, most previous studies required multimodal CT images including CTP or CTA. Some dedicated software packages involve tedious semiautomatic or even manual segmentation. Hence, we propose a new way of calculating NWU that uses only non-enhanced admission CT and does not require CTP, CTA, or segmentation of the ischemic core. We hypothesize that in patients with ischemic stroke due to MCA occlusion, a non-enhanced admission CT can be used to predict MCE by calculating NWU through pre-defined image patches on the affected and non-affected MCA areas. Moreover, combining NWU with clinical and imaging features enables the construction of radiomics models that can predict MCE at an early stage after an ischemic MCA stroke.

## MATERIALS AND METHODS

### Participants and the Dataset

This retrospective single-center study was approved by the Medical Ethics Committee of the General Hospital of Northern Theater Command and no informed consent was required by the committee. The selection of patients was carried out in accordance with inclusion and exclusion criteria. The inclusion criteria for this study were the following: (1) patients who were diagnosed with an MCA infarction with the occlusion at the MCA M1 segment; (2) patients that had both non-enhanced CT images within 24 h on admission and non-enhanced CT images after 24 h as the follow-up scan; (3) demographic information was available from the time of the stroke onset to the CT scans, including NIHSS score, the use of interventional thrombectomy (IT), the use of bone flap surgery, and the outcome (death for stroke or not); and (4) the development of an MCE was known. Using these criteria, we selected 125 patients from archive data on patients who were admitted to the General Hospital of Northern Theater Command between April 2017 and December 2018. Nine patients were further excluded due to the poor quality of admission CT images at 24 h. Finally, a total of 116 patients were included in the study.

We declared patients to have an MCE if they had infarcts with a mass effect during the follow-up non-contrast CT after admission, had clinically experienced a cerebral hernia due to the mass effect of edema, received bone flap surgery, or died due to the mass effect. This definition is the same as that given by Broocks et al. (16).

CT images were acquired with a Discovery CT750 HD scanner (GE Healthcare, Milwaukee, WI, USA) with a tube voltage of 120 kVp, x-ray tube current of 300 mA, the protocol of Axial Head, a slice thickness of 5.0 mm, 20 mm spacing between slices, a matrix of 512 × 512, and voxel spacing of 0.449/0.449 mm. The CT image data is available upon request after approval from the General Hospital of Northern Theater Command, China.

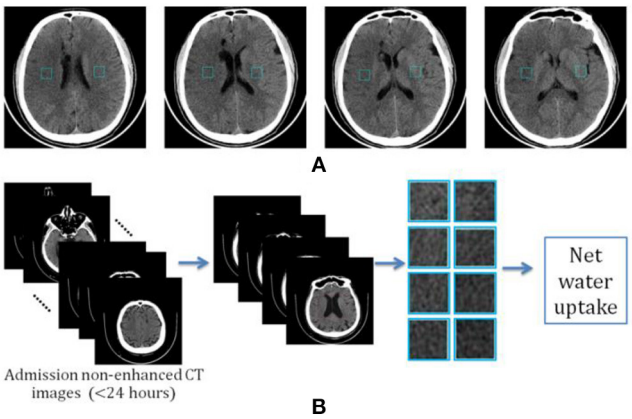


**FIGURE 1 |** Determination of image patch-based net water uptake (IP-NWU). **(A)** The standard reference images with patches of 30 × 30; **(B)** The procedure for calculating IP-NWU.

## Net Water Uptake Calculated by Image Patches

Given the fact that an early hypoattenuated infarct (lesion core) is often not visible or that it can be difficult to precisely locate in non-enhanced CT images, we propose a new way of calculating net water uptake using CT patches determined using the standard reference images. After reviewing all the images, two experienced neuroradiologists selected four slices as the standard reference images and marked two mirrored patches of 30 × 30 voxels from the right and left MCA areas at each slice, as shown in **Figure 1**.

The criteria for determining the reference images included: (1) that patches should be located in the upper temporal lobe, the lateral parietal lobe, or the border area of the frontal, temporal, and parietal lobes; (2) the patches should avoid old lesions; (3) that patches should be located in the infarct area if there is an obvious infarct area; and, (4) the regions with CSF should be avoided to eliminate its effect on NWU. Subsequently, blinded to any clinical information, two other neuroradiologists independently located four pairs of patches from the images of each patient using these reference images and following the criteria mentioned above simultaneously.

Among each pair of patches, the example with hypoattenuation was considered to be ischemic and became density (HU) of $D_{Ischemic}$; the other was the normal patch with the density of $D_{Normal}$. Image patch-based net water uptake (IP-NWU) was calculated with the formula:

$$IP - NWU = 1 - \frac{D_{Ischemic}}{D_{Normal}}. \quad (1)$$

## Net Water Uptake Calculated by Segmented Regions

We determined another way of calculating NWU by manually segmenting the ischemic regions. The result was named the segmented region-based NWU (SR-NWU). As shown in **Figure 2**, first, both the admission CT images (<24 h; Image-A) and the follow-up CT images (>24 h; Image-F) were aligned and normalized to MNI-152 space by linear affine transformation with 12 degrees of freedom. Second, four slices were selected from Image-F using standard reference images and the ischemic regions were manually segmented. Finally, these regions were overlaid onto Image-A to calculate $D_{Ischemic}$ from the CT intensity in Image-A, and $D_{Normal}$ was determined from the mirrored region.

## Histogram Based Imaging Features

To fully utilize the information contained in the selected patches, we also calculated the voxel-wised IP-NWU maps ($\frac{D_{Ischemic}}{D_{Normal}}$, four 30 × 30 matrices with elements ranging from 0 to 1.0). Based on the four maps, the discrete histogram function can be depicted as

$$h(r_n) = Y_n \quad (2)$$

where $r_n$ is IP-NWU of the $n$-th grade, $Y_n$ is the number of voxels with IP-NWU of $r_n$, $n$ =1, 2, .., N. Here N was set at 8.

For univariate data $Y_1$, $Y_2$, ..., $Y_N$, five parameters could be calculated: (1) standard deviation ($s$); (2) slope; (3) entropy; (4) skewness ($g$); and (5) kurtosis. The slope was defined as the gradient between the minimum and maximum points among the vector of $Y_1$, $Y_2$, ..., $Y_N$. Entropy was defined as

$$H = \sum_{n=1}^{N} p_n \log p_n \quad (3)$$

where $p_n$ is the ratio of the number of voxels with IP-NWU of $r_n$ to the total number of voxels. $H$ indicates the average amount of information in the image. The skewness was defined as

$$g = \frac{\sum_{i=1}^{N} \left(Y_i - \overline{Y}\right)^3 / N}{s^3} \quad (4)$$

where $s$ is the standard deviation and $\overline{Y}$ is the mean. The skewness was near zero for the symmetric data, negative for the data skewed left, and positive for the data skewed right. The kurtosis is given as

$$k = \frac{\sum_{i=1}^{N} \left(Y_i - \overline{Y}\right)^4 / N}{s^4} - 3 \quad (5)$$

Hence, $k$ is zero for the standard normal distribution; it is positive for a "heavy-tailed" distribution and negative for a "light-tailed" distribution.

In total, 13 image features including $Y_1$, $Y_2$, ..., $Y_8$, and the five parameters defined above were employed to construct the radiomics models for predicting MCE. The calculation of 13 radiomics features was done using the Python code written by our group.

## Machine Learning Algorithms

Three machine learning algorithms including support vector machine (SVM), logistic regression (LR), and random forest (RF) were employed as the classifier to predict MCE using IP-NWU,

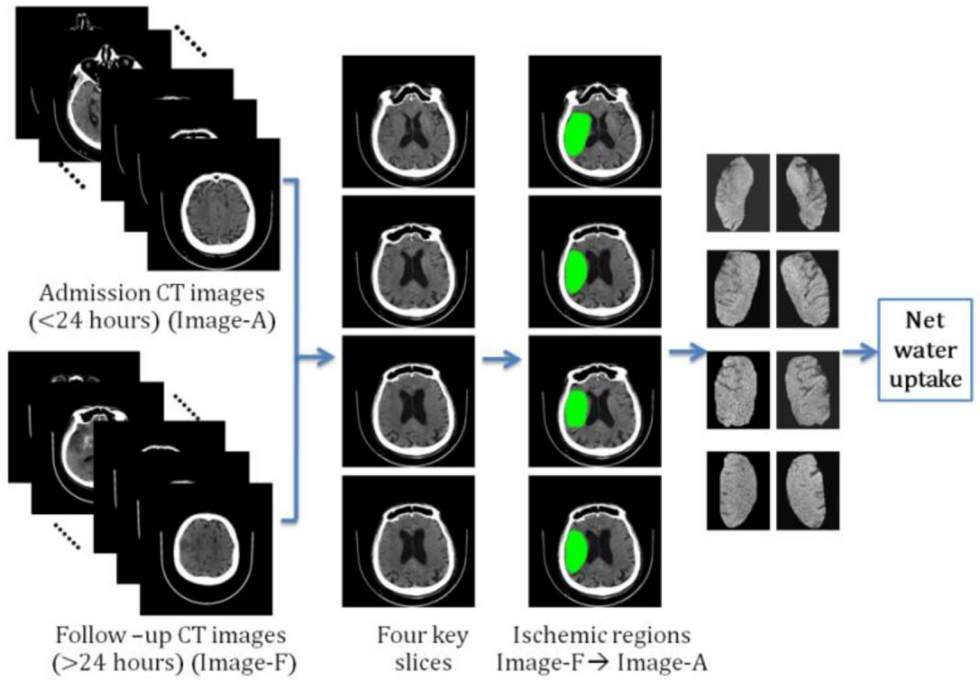


**FIGURE 2 |** The procedure for calculating segmented region-based net water uptake (SR-NWU).

13 image features, and three clinical features (age, gender, and NIHSS score).

For a training dataset $D = \{(x_1, y_1), (x_2, y_2), \ldots, (x_m, y_m)\}$, $y_i \epsilon \{-1, +1\}$, the SVM algorithm draws each entity $(x_i, y_i)$ in the dataset as a point in n-dimensional space ($n$ is the number of features) and each feature is treated as a specific coordinate. The classification is carried out by finding a hyperplane $(\omega, b)$ that maximizes the margin between two categories (23–25). The learned parameters $\omega$ and $b$ can be determined by solving the following equations.

$$\min_{\omega,b} \frac{1}{2} \|\omega\|^2 \tag{6}$$

$$s.t.\ y_i \left(\omega^T x_i\right) \geq 1,\ i = 1,\ 2,\ \ldots,\ m. \tag{7}$$

LR is a kind of classic supervised learning method and it models the log odds (or logit) by linearly combining the independent variables (26).

$$\ln\left(\frac{y}{(1-y)}\right) = \omega^T x + b \tag{8}$$

For a dataset $\{(x_i, y_i)\}_{i=1}^m$, $y_i \epsilon \{0, 1\}$, LR estimates $\omega$ and $b$ by maximizing the log-likelihood

$$l(\omega, b) = \sum_{i=1}^{m} \ln p\left(y_i | x_i; \omega, b;\right) \tag{9}$$

where

$$p(y = 1|x) = \frac{e^{w^T x+b}}{1 + e^{w^T x+b}} \tag{10}$$

$$p(y = 0|x) = \frac{1}{1 + e^{w^T x+b}} \tag{11}$$

RF is a parallel-style ensemble learning method that uses a decision tree as the base learner and bagging as the ensemble strategy (27, 28). Each bootstrap sample generated through bagging with $m$ observations was used to train one decision tree and a final consensus estimate was obtained by combining all individual bootstrap estimates. A subset $p$ of $n$ features was selected randomly for the partition of each node of the tree, which effectively reduced the similarity of trees generated from different bootstrap samples (29). One can refer to the specific literature on machine learning for more details about SVM, LR, and RF (30).

All three machine learning algorithms were implemented with Scikit-learn (an open source machine learning library) with default settings. Regarding the RF classifier, there was hyperparameter tuning and cross validation. Specifically, the optimal values of two hyperparameters of random_state and n_estimators were determined with a grid search: for random_state, a range of 2–16 with a step of 2 was used, and for n_estimators, a range of 100–1,000 with a step of 100 was used. The final optimal parameters were random_state = 10 and n_estimators = 100.

## Statistics and Performance Evaluation of Predictive Models

The inter-reader agreement for IP-NWU was evaluated with the intraclass correlation coefficient (ICC). If the ICC is larger than 0.75, then the reliability of the method for calculating NWU is good. The Bland-Altman statistical method was applied to assess the agreement between two methods of calculating NWU. For IP-NWU, the inter-reader and interoperation agreement were also assessed with the Bland-Altman method. A $p$-value of $<0.05$ was considered to indicate a significant difference.

The performances of various predictive models were evaluated with leave-one-out cross validation (LOOCV). It was implemented with Scikit-learn. In LOOCV, for a dataset with **m** samples, only one sample was left for the test and the others were used for training a model. This process was conducted for **m** times. LOOCV has been shown to almost estimate the generalizability of machine learning models impartially (31).

The receiver operating characteristic curve (ROC), the area under the ROC curve (AUC), the confusion matrix, accuracy (ACC), sensitivity (SEN), specificity (SPC), F1-score, positive predictive value (PPV), and negative predictive value (PPV) were calculated and compared. DeLong's method was used to evaluate whether there was a significant difference between two AUCs of ROC curves (32). Matthews correlation coefficient (MCC) was also used to evaluate and compare the performance of binary classifiers since it considers all fields of the confusion matrix (33).

# RESULTS

## Clinical Characteristics

Among all 116 patients, 39 patients (13 female, 33.3%) were observed with MCE and 77 patients (32 female, 41.6%) were without MCE. There was no significant difference in NIHSS scores between groups with MCE and without MCE [median, 12; interquartile range (IQR), 7 vs. median, 15; IQR, 4.5; $p = 0.2288$]. The time from stroke onset to the first CT scan was longer in patients with MCE (mean 8.28 h vs. mean 5.32 h; $p < 0.05$). However, the time from stroke onset to the second CT scan was equivalent for the two groups (mean 35.42 h vs. mean 36.90 h; $p > 0.05$). The rate of IT was only 15.52% (18 of 116, 4 in the MCE group, 14 in the non-MCE group). Among the 18 patients treated with IT, 11 had achieved complete perfusion and 7 had achieved partial perfusion according to the Thrombolysis in Cerebral Infarction perfusion (TICI) scale (34). The four patients in the MCE group achieved complete perfusion after IT treatment. All the above characteristics of patients are listed in **Table 1**.

## IP-NWU and Its Value With Time

IP-NWU in patients who developed MCE was significantly higher than that in those without MCE ($p < 0.05$; **Figure 3A**). The average of IP-NWU in these two groups was 18.2 and 8.5%. These values were very close to those given by a previous study (18.0 and 7.0%) where semiautomatic segmentation of core lesions was done with the aid of CT perfusion images (16).

IP-NWU in both groups increased from the time of onset to imaging (**Figure 3B**). However, the edema rate for the group with MCE was larger than that of the group without MCE.

## IP-NWU as a Predictor of MCE and the Influence of IT and Time on Predictions

The optimal cut-off value of IP-NWU for discriminating between the patients with MCE and without MCE was 12.25%. Using this cut-off value, the predictive model could achieve a SEN of 0.64, an SPE of 0.91, and an ACC of 0.82. Univariate ROC curve analysis of IP-NWU resulted in an AUC of 0.86 (**Figure 4A**).

As for ROC curve predictions of MCE by IP-NWU, there was no significant difference between groups including and excluding patients who underwent IT (DeLong test, $p > 0.05$; MCC, 0.58 vs. 0.55; **Figure 4A**). This result demonstrated that interventional thrombectomy does not influence the prediction of MCE when using IP-NWU. These findings are in accordance with previous observations (16).

The predictive power of IP-NWU/time and IP-NWU/log(time+1) was not higher than that of IP-NWU, according to the ROC curves shown in **Figure 4B** (DeLong test, $p > 0.05$). MCC was 0.49 and 0.54 for IP-NWU/time and IP-NWU/log(time+1), respectively. Broocks et al. reported a similar result (16).

## Image Patches vs. Segmented Regions

As for the value of NWU, there was no significant difference between the methods of image patches and segmented regions (Bland-Altman test, $p > 0.05$; **Figure 5A**). Most points of difference (113 of 116) were located within the 95% limits of agreement (1.96 standard deviation).

In terms of the prediction of MCE, as shown in **Figure 5B**, IP-NWU had better performance than SR-NWU (AUC: 0.85 vs. 0.83). However, no significant difference was observed (DeLong test, $p > 0.05$; MCC, 0.58 vs. 0.55). Using the comparison of confusion matrices, one also can find that IP-NWU had higher SEN (0.64 vs. 0.56), SPE (0.91 vs. 0.90), and ACC (0.82 vs. 0.78) than SR-NWU (**Figures 5C,D**).

## Inter-reader and Interoperation Agreement of IP-NWU

As for the method of IP-NWU, there was an exceptional inter-reader agreement (ICC is 0.92). The Bland-Altman method also indicated that there was no significant difference between Researcher A and Researcher B regarding the measurement of IP-NWU ($p > 0.05$; **Figure 6A**). Most points were located within the 95% limits of agreement. Meanwhile, as shown in **Figure 6B**, no significant difference was observed between the two measurements by the same reader ($p > 0.05$), indicating good reproducibility of the image patch method. The ICC of the two measurements was 0.95.

## Radiomics Model for Predicting MCE

As shown in **Table 2**, for all three machine learning algorithms, SVM, LR, and RF adding the clinical information of age, gender,

**TABLE 1 |** Characteristics of patients with a middle cerebral artery ischemic stroke.

| Characteristic | Patient with MCE, $n = 39$ | Patients without MCE, $n = 77$ | $p$ |
|---|---|---|---|
| Demographics | | | – |
| Age, year, mean (SD) | 64.23 (±11.39) | 65.79 (±12.05) | 0.5993[a] |
| Women, No. [%] | 13 [33.3%] | 32 [41.6%] | 0.3059[b] |
| NIHSS score | | | 0.2288[a] |
| Median (IQR) | 12 (±7) | 15 (±4.5) | – |
| Mean (SD) | 11 (±6.83) | 15 (±2.94) | – |
| With IT, No. [%] | 4 [21.1%] | 14 [18.2%] | 0.2654[b] |
| Time from stroke onset to the first CT scan (within 24 h), hour, mean (SD) | 8.28 (±6.53) | 5.32 (±4.11) | 0.0038[a] |
| Time from stroke onset to the second CT scan (beyond 24 h), hour, mean (SD) | 35.42 (±8.83) | 36.90 (±10.70) | 0.4600[a] |

*MCE, Malignant cerebral edema; CT, Computed tomography; IT, Interventional thrombectomy; NIHSS, National Institutes of Health Stroke Scale; SD, Standard deviation; IQR, Interquartile range.*
*[a]Two-sample t-test; [b]Chi-squared test.*

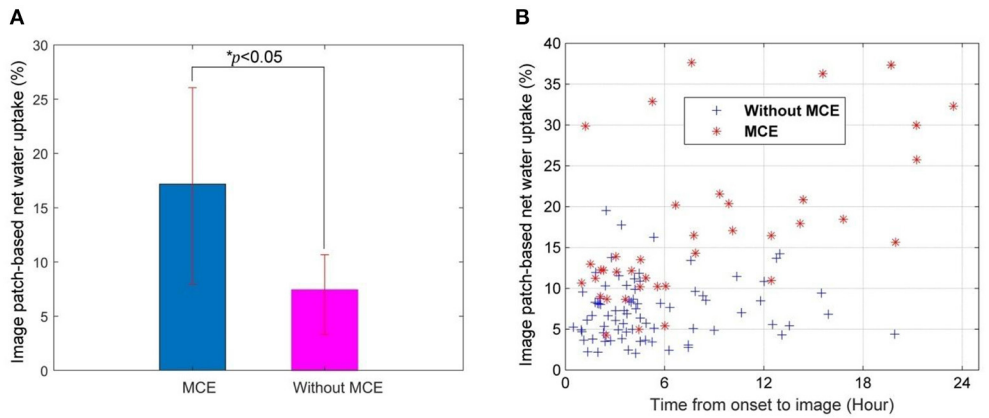


**FIGURE 3 |** Image patch-based net water uptake (IP-NWU) and its relationship with time. **(A)** IP-NWU comparison between patients with MCE and without MCE; **(B)** The relationship between IP-NWU and time from stroke onset to imaging.

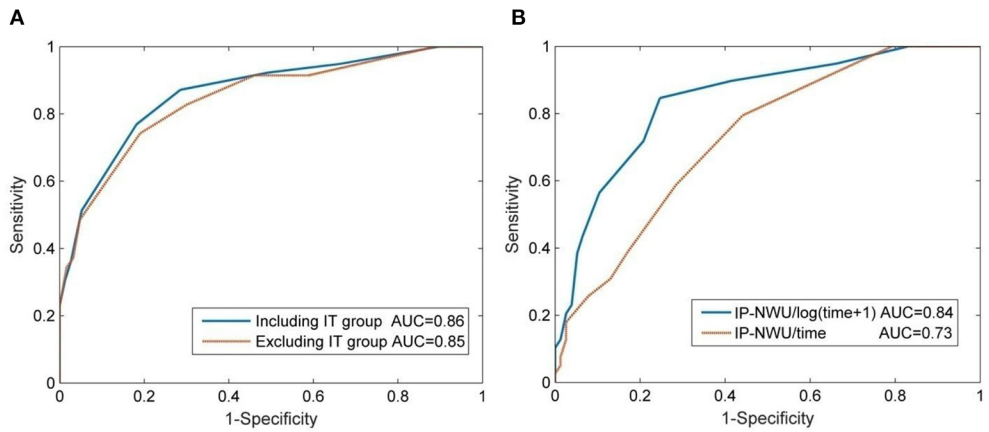


**FIGURE 4 |** Prediction of malignant cerebral edema (MCE) by IP-NWU and its confounders. **(A)** ROC curve of prediction of MCE by IP-NWU for groups including patients who underwent interventional thrombectomy (IT) and excluding patients who underwent IT; **(B)** ROC curve by IP-NWU/time and by IP-NWU/log(time+1).

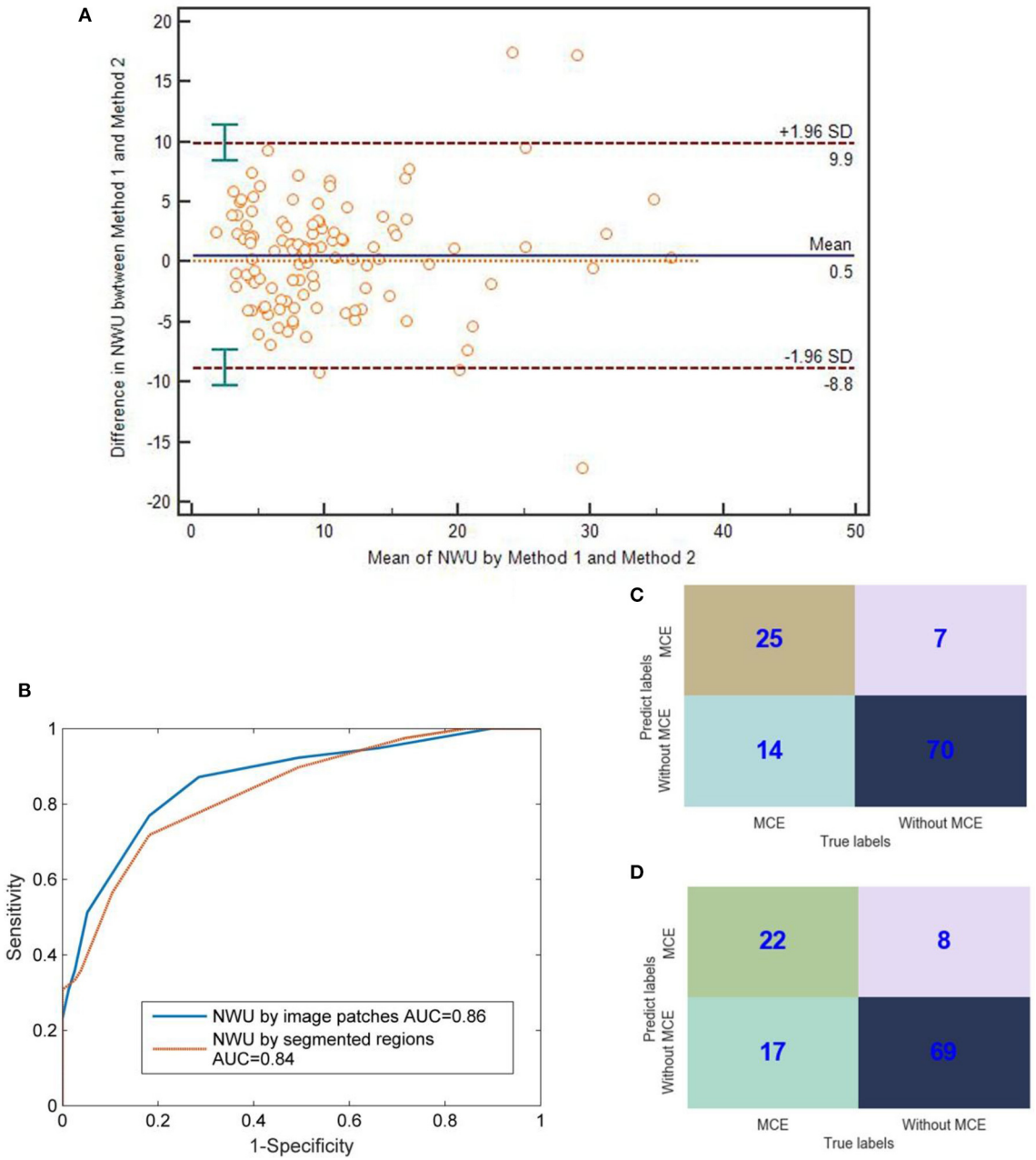


**FIGURE 5 |** Comparison between IP-NWU and SR-NWU and their predictive performances for malignant cerebral edema (MCE). **(A)** Consistence of IP-NWU and SR-NWU; **(B)** ROC curves of MCE prediction by IP-NWU and SR-NWU; **(C)** The confusion matrix of MCE prediction by IP-NWU; **(D)** The confusion matrix of MCE prediction by SR-NWU.

and NIHSS scores of the patients onto IP-NWU did not improve prediction of MCE. For SVM and LR, compared with the prediction when only using IP-NWU, neither features of "NWU + Imaging" nor "NWU + Clinical + Imaging" improved the performance of predicting MCE.

However, as for RF, the features of "NWU + Imaging" can significantly increase the ACC to 0.91, SEN to 0.85, SPE to 0.94, AUC to 0.96, F1-score to 0.90, PPV to 0.87, NPV to 0.92, and MCC to 0.79 (**Table 2**, **Figure 7**; DeLong test, $p < 0.05$). When adding the clinical information, no significant improvement was observed (DeLong test, $p > 0.05$; MCC, 0.80 vs. 0.79). This means that the performance of the radiomics model for predicting MCE depends on both the classifiers and features. In the current study the combination of RF and features of "NWU + Clinical + Imaging" had the best performance. For this model, 73 of 77 patients who did not develop MCE were

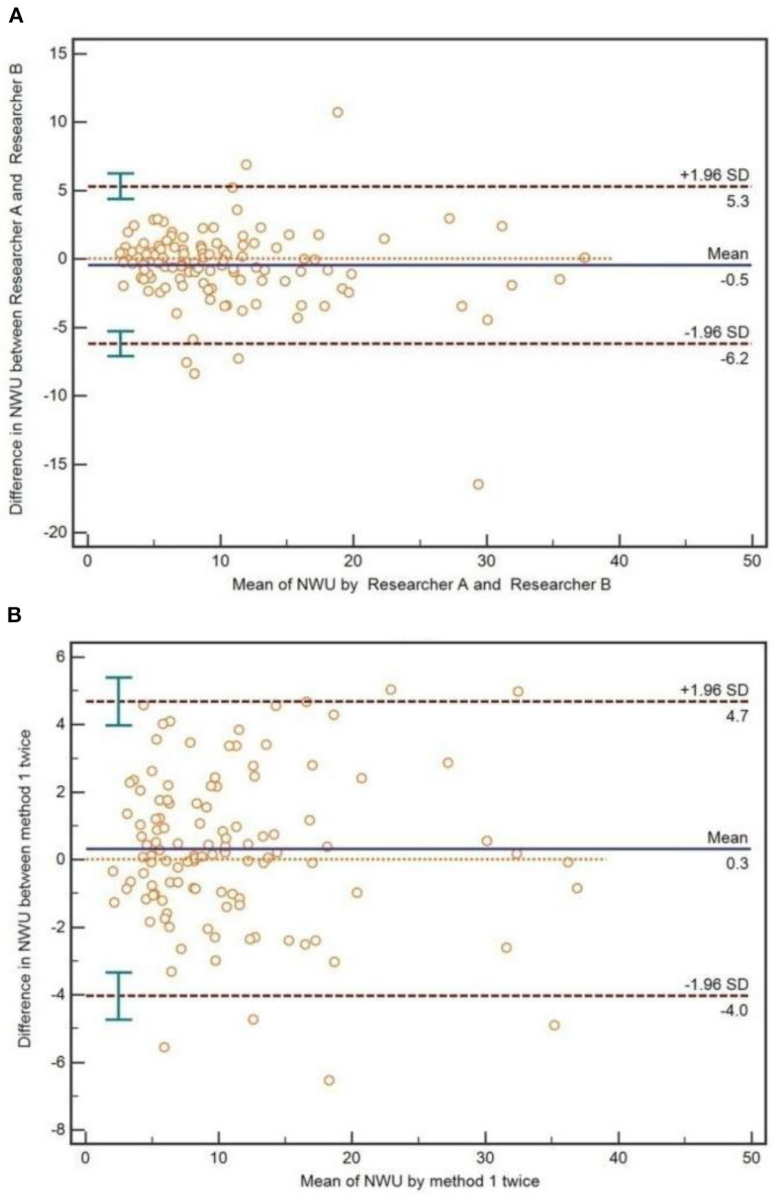


**FIGURE 6 |** Inter-reader and interoperation agreement for image patch-based net water uptake (IP-NWU). **(A)** The inter-reader agreement, evaluated by the Bland-Altman method; **(B)** The interoperation agreement, evaluated by the Bland-Altman method.

accurately predicted and 33 of 39 patients who developed MCE were accurately predicted.

## DISCUSSION

The aim of this study was to calculate net water uptake (NWU) using admission non-enhanced CT image patches scanned within 24 h from stroke onset and build predictive models for MCE by combining NWU with other features using a radiomics approach. The main findings had four aspects: (1) NWU can be estimated by using the standard reference images and patches; (2) the results for IP-NWU showed no significant difference with results when using segmented regions; (3) IP-NWU is a predictor of MCE; and, (4) radiomics models using IP-NWU and other imaging features can predict MCE rather precisely.

### Standard Reference Images and Patches: An Exceptional Method for Calculating Net Water Uptake

Net water uptake in the ischemic regions was originally proposed to identify patients with stroke onset within 4.5 h (the time window of thrombolysis) and extended to predict malignant

**TABLE 2 |** Performance comparison of different radiomics models for predicting MCE.

| Classifier | Features | ACC | SEN | SPE | AUC | F1-score | PPV | NPV |
|---|---|---|---|---|---|---|---|---|
| SVM | NWU + Clinical | 0.80 | 0.62 | 0.88 | 0.85 | 0.72 | 0.72 | 0.82 |
| | NWU + Imaging | 0.84 | 0.64 | 0.94 | 0.84 | 0.85 | 0.83 | 0.84 |
| | NWU + Clinical + Imaging | 0.83 | 0.62 | 0.94 | 0.84 | 0.80 | 0.83 | 0.83 |
| LR | NWU + Clinical | 0.80 | 0.59 | 0.91 | 0.85 | 0.72 | 0.77 | 0.81 |
| | NWU + Imaging | 0.80 | 0.59 | 0.91 | 0.83 | 0.72 | 0.77 | 0.81 |
| | NWU + Clinical + Imaging | 0.81 | 0.62 | 0.91 | 0.81 | 0.73 | 0.78 | 0.82 |
| RF | NWU + Clinical | 0.77 | 0.62 | 0.84 | 0.83 | 0.74 | 0.67 | 0.81 |
| | NWU + Imaging | 0.91 | 0.85 | 0.94 | 0.96 | 0.90 | 0.87 | 0.92 |
| | NWU + Clinical + Imaging | 0.91 | 0.85 | 0.95 | 0.96 | 0.91 | 0.89 | 0.92 |

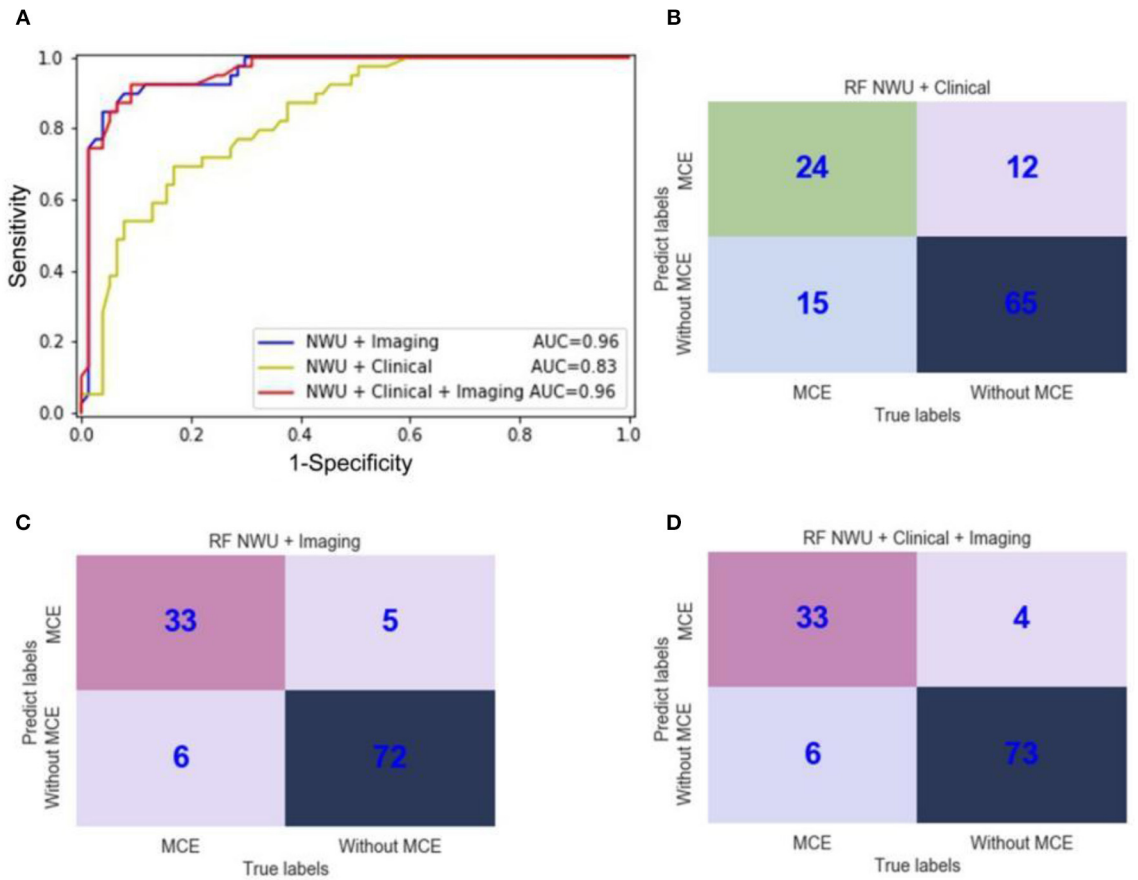


**FIGURE 7 |** ROC curves and confusion matrices of three random forest (RF) radiomics models for the prediction of malignant cerebral edema (MCE). **(A)** ROC curves of three RF radiomics models with different features; **(B)** The confusion matrix for a model with RF and features of "NWU + Clinical;" **(C)** The confusion matrix for a model with RF and features of "NWU + Imaging;" **(D)** The confusion matrix for a model with RF and features of "NWU + Clinical + Imaging".

infarction in 2018 (15, 16). It relies on the high sensitivity of CT perfusion to precisely locate the infarct core and the high specificity of non-enhanced CT to measure density. However, for many stroke centers and patients, the CTP and its postprocessing for quantitative perfusion maps, including cerebral blood volume, cerebral blood flow (CBF), mean transit time (MTT), and time to drain (TTD), are not accessible.

The early hypoattenuation of the ischemic core in non-enhanced CT images is uncertain or difficult to detect. However, the anatomic location of the MCA (the potential target of infarction) is known. Therefore, we proposed a way of calculating NWU using the standard reference images and patches. Our results showed that this method enables presenting a significant difference in NWU between patients with MCE

and without MCE. Further study of the inter-reader agreement in NWU calculation demonstrated that the method had good reproducibility. In summary, using the standard reference images and patches is an exceptional way of calculating net water uptake. It is easy to implement, reliable, and does not require the aid of CTP, CT angiography, or manual segmentation.

Recently, NWU has been used to quantify the treatment effects for ischemic stroke; e.g., thrombectomy and adjuvant drugs, especially for the cases with uncertain indications for treatment, such as low ASPECTS (35). Therefore, IP-NWU may be extended to similar applications.

## Reference Images and Patches vs. Segmented Ischemic Regions

Locating the infarct core by overlaying segmented ischemic regions from follow-up CT images (>24 h after stroke onset) is an alternative method compared to the standard method of using a CBV map from CTP. No significant difference was observed between IP-NWU and SR-NWU, which supports the evidence that IP-NWU is accurate.

However, it is still not clear to what extent the follow-up CT images can work as surrogates of CTP. The ischemic core, penumbra, and benign oligemia cannot be differentiated from the follow-up CT images (36). The registration error between Image-A and Image-F may have a further detrimental effect on NWU calculations.

## Predictor of MCE and Other Confounders

IP-NWU can be a predictor of MCE for middle cerebral artery stroke patients with an AUC of 0.85. Moreover, the prediction was not influenced by interventional thrombectomy, which is in agreement with a previous study (16). The decision to take IT is based on an early infarct and hypoattenuation. Specifically, patients with a large volume of early infarct and visually evident areas of hypoattenuation are potentially excluded from IT. However, the recanalization status and its influence on IP-NWU and MCE are unknown and need further investigation (37, 38). Complete recanalization does not directly indicate a good clinical outcome (39). It has been noted that the prediction of MCE is different from that of cerebral edema (40, 41). Moreover, the rate of IT in our current study (15.52%, 18 of 116) might be lower than that in developed countries due to the high economic cost and late presentations at the hospital.

The relationship between IP-NWU and time in patients with MCE and without MCE is also in accord with that reported in a previous study (16); i.e., NWU increases with time from stroke onset. However, there was no significant difference in the AUC for MCE prediction among NWU, NWU/time, and NWU/log(time+1).

## Radiomics Leverages Machine Learning and Features to Predict MCE Precisely

Our radiomics model using RF and features of "NWU+Clinical+Imaging" had a comparable performance with the model reported by Broocks et al. (AUC: 0.96 vs. 0.93) (16). This indicated that using more imaging features might be superior to only using NWU. Moreover, the possible reason may rely on two aspects: (1) CTP was not used to locate the ischemic core; and (2) our data consisted of 33.6% (39 of 116) of patients with MCE, which was higher than that in a study by Broocks et al. (18.2%) (16). Our model also showed a higher AUC than that of EDEMA scores (AUC = 0.72) (10) and that of modified EDEMA scores by adding NIHSS scores for 478 Chinese patients (AUC = 0.80) (11).

Radiomics leverages machine learning and quantitative imaging features to improve the prediction of clinical outcomes (18). For the prediction of MCE in our current study, radiomics worked well. By adding 13 imaging features from histogram analysis of voxel-wised IP-NWU maps, the AUC of the classifier by RF can increase from 0.86 to 0.96. This improvement may be due to the fact that: (1) multivariate analysis by machine learning has more predictive power than the univariate ROC analysis; and, (2) IP-NWU is only the mean of IP-NWU maps, and more measures from these maps represent the characteristics of the core lesions better. The lesion volume, texture features, penumbra pattern, and other high-level abstract features may be helpful and should be included in radiomics models of MCE predictions in the near future.

All 13 imaging features extracted from histogram analysis were used without selection in our current study. Unlike the application of the PyRadiomics Python package in tumor imaging, more than 1,000 features are extracted (https://pyradiomics.readthedocs.io/). Hence feature selection must be done to reduce overfitting. During feature selection, the importance of features can be obtained (42). Since we only used 13 imaging features, feature selection, and importance analysis were not undertaken in this study. The reason why the PyRadiomics Python package was not used to extract more than 1,000 features is that the voxel-wised IP-NWU map has a small size of 30 × 30 voxels. This map does not contain rich information such as the locations of tumor lesions.

For the predictive radiomics model, there is a danger of overfitting if the number of features is very large. In our study, the largest number of features was 19 (IP-NWU, 13 imaging features, and 3 clinical features) and 116 samples or patients were included. According to a rule of thumb in radiomics, each feature requires 10 samples (18). Therefore, the overfitting in our study should be minimal.

In the present study, RF performed better for MCE prediction than SVM and LR. For example, the model using RF and "NWU + Clinical + Imaging" had an AUC of 0.96, while the model using LR and SVM had an AUC of 0.81 and 0.84, respectively. RF usually performs best in situations where the output is highly sensitive to small changes in input (29). This may indicate that the prediction of MCE is highly sensitive to small changes in NWU and imaging features. Moreover, RF is one ensemble or consensus estimator, and thus has the merit of mitigating both underfitting and overfitting (29). Underfitting and overfitting may exist in the current study given the fact that the sample size was small.

Adding the clinical information of age, gender, and NIHSS scores did not significantly improve the prediction of MCE, which agreed with another previous report (16).

## Limitations and Future Works

Our study has some limitations that could provide direction to future studies. First, our study was retrospective and limited to one single center. The relevance of the resulting radiomics models is unknown for data from other hospitals. Second, the number of patients (116) was relatively small, which limits the statistical power of the study. Third, the selection of slices and patches was done by experts, making IP-NWU depend on expert conditions, such as preferences, experiences, and mood. To set image patches in the cortex orientated by ASPECTS regions may further improve the presented method. It is noted that the cortex regions with CSF should be avoided to eliminate the effect of CSF on NWU. This criterion may make some early infarcts in the cortex not represented in the image patches. Finally, we used three machine learning algorithms and manually designed histogram-based imaging features.

A prospective and multi-center study with CTP and non-enhanced CT scans should be carried out in the near future, before the proposed IP-NWU and radiomics models are introduced as clinical applications. The automatic and machine learning based detection of early infarctions from non–contrast-enhanced CT images should be used to help calculate NWU and predict MCE (43, 44). Other features such as texture and high-level abstract representation can be included. As a state-of-the-art example of deep learning, a deep convolutional neural network (DCNN) may help predict MCE directly according to the image patches or infarction regions (45–47). Given the fact that a stroke is a dynamic process, using both admission and follow-up CT images to characterize the temporal and spatial development of infarcts and edema volume may further improve the final prediction of clinical outcomes.

## CONCLUSION

Net water uptake can be calculated based on mirrored patches that are selected by senior neuroradiologists from admission non-enhanced CT images that were scanned within 24 h after stroke onset using standard reference images. The resulting IP-NWU values showed a significant difference between patients with MCE and without MCE and thus it is an effective predictor of MCE. The inter-reader and interoperation agreement for IP-NWU are exceptional. Through integrating IP-NWU and other imaging features by machine learning, the radiomics models further improved the prediction of MCE. In summary, this study demonstrated the feasibility of predicting MCE using only admission non-enhanced CT images scanned within 24 h after onset, even without the aid of CT perfusion or follow-up CT scans. This will potentially help clinicians make decisions about performing a surgical decompressive craniectomy or employing other intensive monitoring to benefit stroke patients.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of General Hospital of Northern Theater Command. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

SQ, YK, YY, and HC designed and directed the study. BF, SQ, LT, HX, BY, and YD analyzed data. LT, HX, and HC recruited participants and acquired data. BY and YD reviewed the CT images and drew the image patches. BF, SQ, YK, and YY drafted the manuscript together. All authors revised and approved the final manuscript.

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# Net Water Uptake Calculated in Standardized and Blindly Outlined Regions of the Middle Cerebral Artery Territory Predicts the Development of Malignant Edema in Patients With Acute Large Hemispheric Infarction

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**Background and purpose:** Previous studies have demonstrated that Net Water Uptake (NWU) is associated with the development of malignant edema (ME). The current study aimed to investigate whether NWU calculated in standardized and blindly outlined regions of the middle cerebral artery can predict the development of ME.

**Methods:** We retrospectively included 119 patients suffering from large hemispheric infarction within onset of 24 h. The region of the middle cerebral artery territory was blindly outlined in a standard manner to calculate NWU. Patients were divided into two groups according to the occurrence of ME, which is defined as space-occupying infarct requiring decompressive craniotomy or death due to cerebral hernia in 7 days from onset. The clinical characteristics were analyzed, and the receiver operating characteristic curve (ROC curve) was used to assess the predictive ability of NWU and other factors for ME.

**Results:** Multivariable analysis showed that NWU was an independent predictor of ME (OR 1.168, 95% CI 1.041–1.310). According to the ROC curve, NWU≥8.127% identified ME with good predictive power (AUC 0.734, sensitivity 0.656, specificity 0.862).

**Conclusions:** NWU calculated in standardized and blindly outlined regions of the middle cerebral artery territory is also a good predictor for the development of ME in patients with large hemispheric infarction.

**Keywords: net water uptake, large hemispheric infarction, malignant edema, area under curve, prediction power**

## INTRODUCTION

Stroke has become a leading cause of mortality and disability worldwide, and it brings huge economic costs and family burdens (1). Acute ischemic stroke accounts for about 80% of all types of stroke (2). Large hemispheric infarction (LHI) is defined as affecting the majority of or complete middle cerebral artery (MCA)

territory with or without anterior cerebral artery and posterior cerebral artery involvement (3). It is a disastrous subtype of acute ischemic stroke, which may lead to life-threatening swelling (4). Furthermore, LHI patients with malignant edema (ME) develop a mortality rate of nearly 40 ∼ 80% under standard treatment, while mortality of those without ME is nearly 5 ∼ 25% (3, 5, 6). It has been demonstrated by previous studies that timely decompressive craniotomy may reduce the mortality of LHI patients with ME (7, 8). Thus, early identification of LHI patients at risk for ME should be anticipated (3, 9).

There have been several studies exploring valid predictors of ME in LHI patients, such as the National Institutes of Health Stroke Scale (NIHSS), presence of hyperdense artery sign, a higher level of blood glucose, decreased level of consciousness, early infarct signs, intracranial cerebrospinal fluid volume, fluid balance variations, collateral circulation (10–17).

Interestingly, in 2018, Broocks' team found that Net Water Uptake (NWU) on baseline Computed Tomography (CT) was an important predictor of ME in LHI patients (9). Since then, accumulating evidence demonstrates that NWU can be used as an important qualified biomarker of edema in ischemic stroke. For example, NWU was used to estimate final infarction volumes (18), which serves as an indicator of "tissue clock" instead of the real "time clock" (19), and predicted the effect of recanalization (20) and early bleeding risk after endovascular treatment, especially with low ASPECTS (21). However, the measurement of NWU in previous studies mainly depends on CT perfusion (CTP) (9, 18–21). However, not all stroke centers have access to CTP in clinical practice. In this study, we aimed to investigate, whether NWU calculated in standardized and blindly outlined regions of the MCA territory is a reliable predictor of ME in patients with LHI.

# METHODS

## Population

The medical records and images of consecutive patients with LHI at Northern Theater General Hospital between October 9, 2017, and July 13, 2020, were reviewed retrospectively. This retrospective study was approved by an institutional review board and informed consent was waived. Patients were screened based on the following inclusion criteria: (1) acute ischemic stroke involving the anterior circulation with non-enhanced CT (NECT) with or without computed tomography angiography (CTA) at admission within 24 h from symptom onset; (2) follow-up NECT or diffusion weighted imaging (DWI) available within 24–48 h from symptom onset; and (3) MCA infarction occupying >1/2 MCA territory confirmed by follow-up CT or DWI; (4) NIHSS >3 at admission. Patients were excluded based on the following exclusion criteria: (1) presence of intracranial or subarachnoid hemorrhage at admission; (2) presence of symptomatic intracranial hemorrhage (SICH) (22) in follow-up CT; (3) preexisting stroke with mRS ≥2; (4) images not qualified enough for measurement due to artifacts; and (5) patients undergoing mechanical thrombectomy (considering the effect on the development of ME). The enrolled patients were separated into the ME group and the non-ME group depending on the presence or absence of ME. According to a previous study (9), ME was defined as a space-occupying infarct requiring decompressive craniotomy or death resulting from cerebral hernia in 7 days from symptom onset.

The following characteristics of patients were recorded at baseline: gender, age, NIHSS, intravenous thrombolysis or not, previous medical history such as atrial fibrillation, hypertension, diabetes, and ischemic stroke, systolic and diastolic blood pressure, blood glucose, the time from onset to the first image.

## Image Acquisition and Analysis

CT scanner (General Electric, Boston, United States of America) was used in this study. The tube settings for NECT were 120 kV and 300 mA per rotation. Slices were reconstructed with a thickness of 5 mm.

All NECT images were outlined and calculated by one experienced neuroradiologist (BQ Yang) and neurologist (HS Chen), separately. The territory of MCA at basal ganglia level was blindly outlined in a standard manner at the infarct side according to clinical evidence. As shown in **Figure 1**, the extension line of the anterior horn of the lateral ventricle was set as the anterior boundary, and the extension line of the posterior horn of the lateral ventricle as the posterior one, while the outer edge of the brain cortex was set as the outer boundary, and inter edge of the caput nuclei caudate and posterior limb of the internal capsule as the inter boundary. Then, the mean density of the outlined MCA territory was measured and recorded as $D_{ischemic}$, while the mean density of a mirrored region at the contralateral side was measured and recorded as $D_{normal}$ using commercially available software (Analyze 14.0, Biomedical Imaging Resource, Mayo Clinic, Rochester, MN). Both density measurements were sampled between 20 and 80 Hounsfield units to avoid intracranial calcifications and cerebral fluid and were eventually used to calculate NWU according to the method reported in a previous study (9).

$$NWU(\%) = (1 - D_{\text{ischemic}}/D_{\text{normal}})^{*}100$$

## Statistical Analysis

Scatterplot was carried out using the open source statistical software RStudio Version 1.3.1093 (Rstudio PBC, Boston, MA), and visualization with the R package ggplot2 (23). Other statistical analyses were performed using SPSS 22.0 for Windows (IBM Corp, Armonk, NY). Quantitative variables were described as mean ± standard deviation (SD), or median and interquartile range (if not normally distributed) while counting data were presented as n (%). To compare the data between the two groups, we used a *t*-test or Mann–Whitney *U*-test (not normally distributed) for quantitative data, and a Chi-square test for counting data. Multivariable logistic regression analysis was used to identify the independent factors associated with ME. The odds ratio (OR) and 95% confidence interval (*CI*) were also calculated. A *P*-value of <0.05 in two tails was considered to be significant. Receiver operating characteristic (ROC) curves and area under curve (AUC) were calculated, respectively, to assess the ability of the factors in identifying patients with ME.

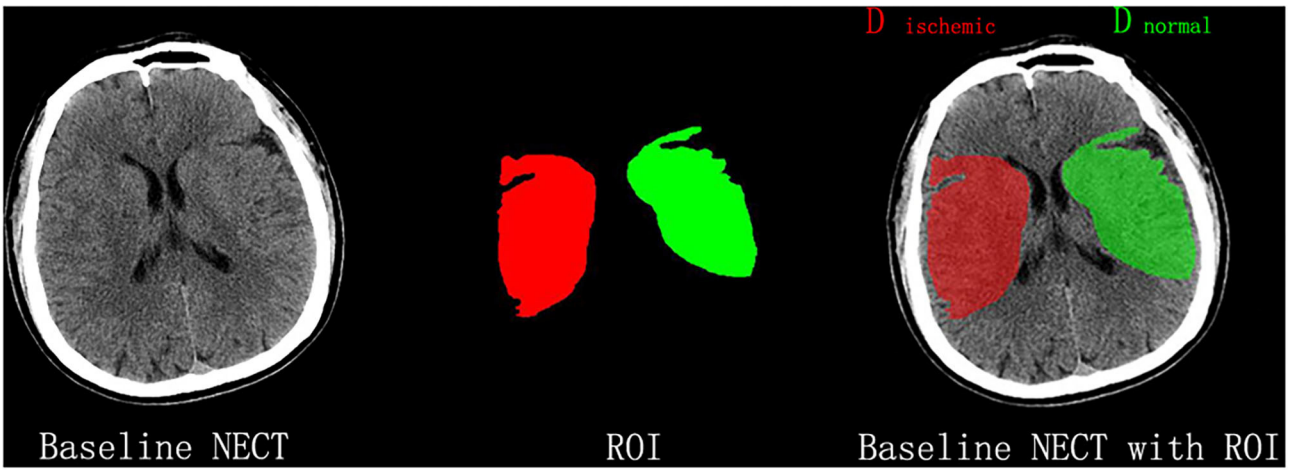


**FIGURE 1 |** Measurement of NWU on admission nonenhanced computed tomography (NECT). According to the clinical manifestations, the infarct lesion occurred in the right middle cerebral artery territory, which was blindly outlined. The mean density of the territory (Dischemic) and a mirrored contralateral region of interest (Dnormal) was then measured to calculate NWU.

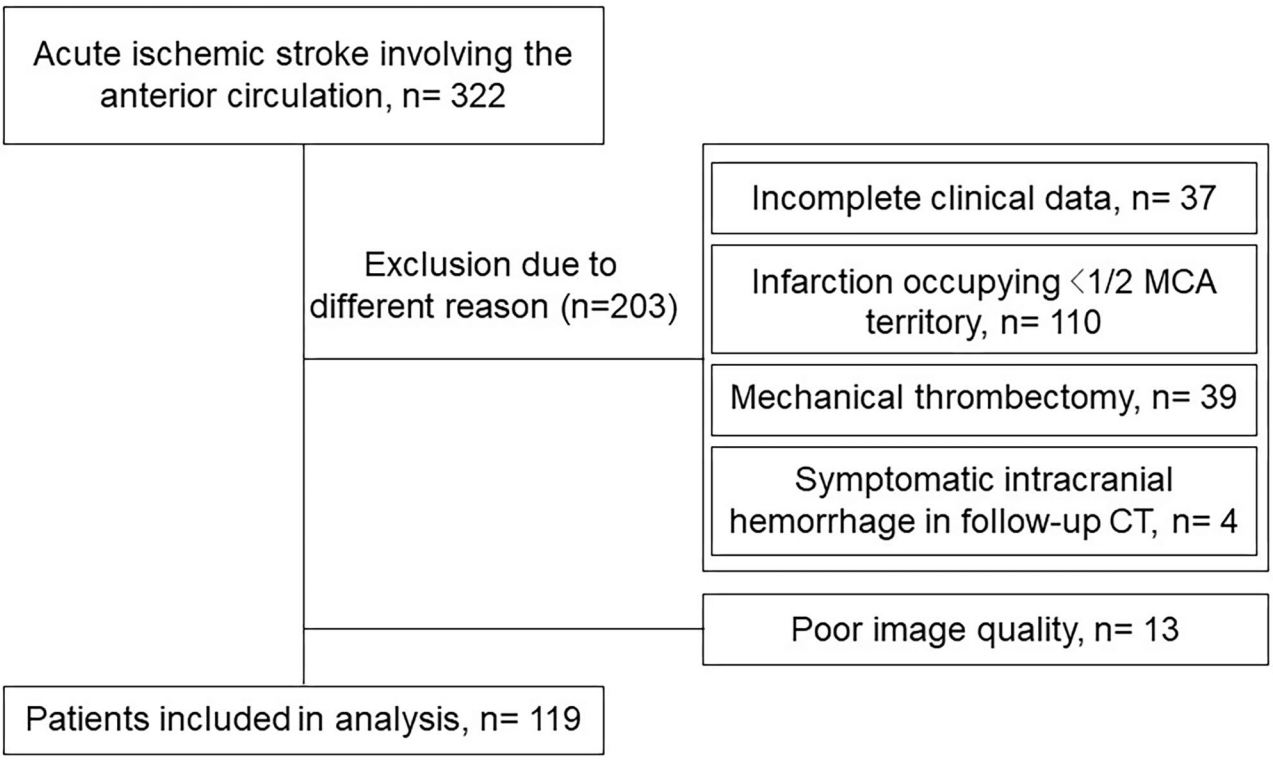


**FIGURE 2 |** Flow chart with application of inclusion and exclusion criteria.

The whole cohort was separated into six groups according to time windows (the time from onset to first image), that is 0–3 h, 3–6 h, 6–9 h, 9–12 h, 12–15 h, 15–24 h. ROC curves were used to assess the predictive ability of NWU in each time window in identifying ME. In addition, a scatterplot was used to show the possible relationship between NWU and the time from onset to first image. Two models reported in a previous study (9) were used to investigate if NWU is more likely to be linear-related with the time from onset to first image in 24 h. One model is NWU= b* time, stating that NWU is linear-related with the time from onset to first image. The other is NWU= b* log (time+1), representing a non-linear relation. Thus, NWU/time

**TABLE 1 |** Comparison of baseline characteristics between non-ME and ME groups.

| Characteristics | Non-ME group ($n = 87$) | ME group ($n = 32$) | *P*-value |
|---|---|---|---|
| Female (%) | 31 (35.63) | 14 (43.75) | 0.418 |
| Age, mean (SD) | 66.69 (±11.82) | 68.56 (±10.54) | 0.432 |
| NIHSS at admission, median (IQR) | 14 (11–18) | 18 (13–20) | 0.003 |
| IVT (%) | 35 (40.23) | 9 (28.13) | 0.225 |
| Atrial fibrillation (%) | 39 (44.83) | 16 (50) | 0.616 |
| Hypertension (%) | 48 (55.17) | 21 (65.63) | 0.306 |
| Diabetes (%) | 18 (20.69) | 7 (21.88) | 0.888 |
| Pre-ischemic stroke (%) | 15 (17.24) | 3 (9.38) | 0.288 |
| SBP, median (IQR) | 162 (145–177) | 161 (148–185) | 0.484 |
| DBP, median (IQR) | 90 (80–97) | 90 (82–109) | 0.332 |
| Blood glucose, median (IQR) | 7.72 (6.25–9.77) | 7.56 (6.11–9.23) | 0.958 |
| OFT, median (IQR) | 4.28 (2.23–8.02) | 7.01 (2.65–13.55) | 0.039 |
| NWU, median (IQR) | 4.65 (1.51–7.41) | 9.74 (3.24–12.52) | <.0.01 |

*SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; IVT, intravenous thrombolysis; SBP, systolic blood pressure; DBP, diastolic blood pressure; OFT, time from onset to first image; NWU, Net Water Uptake.*

and NWU/log (time+1) were also tested together with absolute NWU as predictors of ME (9).

## RESULTS

We continuously screened 322 patients from our stroke registry database. We excluded 203 patients due to different reasons including incomplete clinical data, infarction occupying <1/2 MCA territory, mechanical thrombectomy, symptomatic intracranial hemorrhage in follow-up CT (**Figure 2**). Finally, 119 patients were recruited for the analysis including the non-ME group ($n = 87$) and ME group ($n = 32$). As shown in **Table 1**, NIHSS at admission, the time from onset to first image, NWU in ME group were higher than those in the non-ME group ($P < 0.05$), while there is no significant difference in other characteristics between two groups.

The multivariable logistic regression analysis showed that NWU (OR: 1.168, 95% CI: 1.041–1.310) and NIHSS (OR: 1.121, 95% CI: 1.006–1.250) were significantly associated with ME, but not the time from onset to first image and tPA thrombolysis (**Table 2**).

ROC curves and AUC were also calculated to assess the prediction power of the factors mentioned above in identifying patients with ME. As shown in **Figure 3**; **Table 3**, NWU showed better performance at predicting the occurrence of ME with a higher AUC (0.734) than that of NIHSS at admission. The cutoff value, sensitivity, and specificity were exhibited in **Table 3**.

To investigate the possible association of the time from onset to first image with the prediction ability of NWU, the patients were further divided into six groups according to time windows.

**TABLE 2 |** Multivariable logistic regression analysis of NWU, NIHSS at admission, the time from onset to first image, and IVT.

| Factors | B | S.E. | OR | 95% *CI* | *P*-value |
|---|---|---|---|---|---|
| NWU | 0.155 | 0.059 | 1.168 | 1.041–1.310 | 0.008 |
| NIHSS at admission | 0.115 | 0.055 | 1.121 | 1.006–1.250 | 0.038 |
| OFT | 0.005 | 0.049 | 1.005 | 0.913–1.105 | 0. 925 |
| IVT | −0.362 | 0.501 | 0.696 | 0.260–1.860 | 0.470 |

*NIHSS, National Institutes of Health Stroke Scale; NWU, Net Water Uptake; OFT, time from onset to first image; IVT, intravenous thrombolysis; OR, odds ratio; 95% CI, 95% confidence interval.*

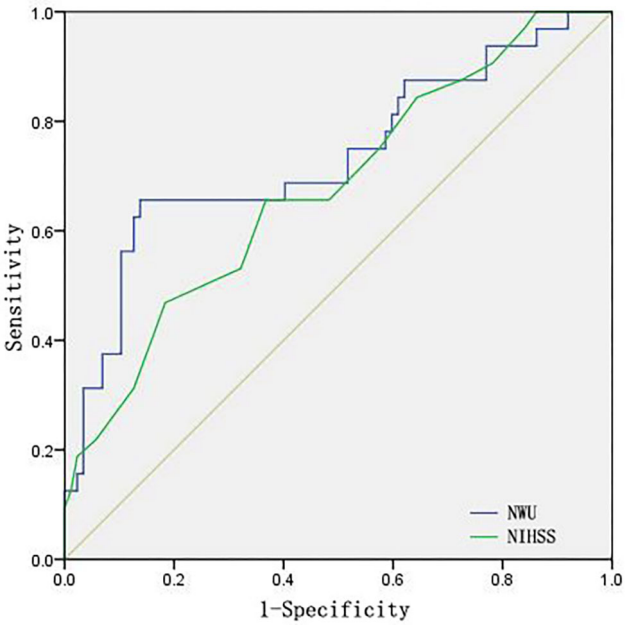


**FIGURE 3 |** ROC curves of NWU and NIHSS at admission.

**TABLE 3 |** Predictive values of AUC.

| Factors | AUC | Cutoff | Sensitivity | Specificity |
|---|---|---|---|---|
| NWU | 0.734 | 8.127 | 0.656 | 0.862 |
| NIHSS at admission | 0.677 | 17 | 0.656 | 0.632 |

*NIHSS, National Institutes of Health Stroke Scale; NWU, Net Water Uptake; AUC, area under curve.*

As shown in **Table 4**, NWU in the time window of 3–6 h showed a poor predictive value (AUC: 0.500).

Similar to the results of AUC, when the time from onset to first image was settled at the period from 3 to 6 h, the fitting line of the ME group and the non-ME group was too close to discriminate (**Figure 4**), suggesting that there may exist the time window of NWU predicting the occurrence of ME.

Absolute NWU, NWU/time, and NWU/log (time+1) were also assessed through ROC curves and used to identify patients at risk of ME. As shown in **Figure 5**, NWU and NWU/log (time+1)

exhibited better predictive power than NWU/time (NWU: 0.734, NWU/log (time+1): 0.676, NWU/time was 0.575).

## DISCUSSION

Recent studies have shown that NWU is an important surrogate marker for the development of ME (9, 18, 19), but NWU calculation depended on CTP, which was used to detect the infarction area. The current study is the first attempt to calculate NWU based on the standardized and blindly outlined regions of MCA. The results showed that NWU calculated with this method also exhibited a good predictive value (AUC: 0.734) in identifying ME, although the predictive power was not as strong as that in a previous study (AUC: 0.93) (9).

The current method is not as accurate as the previous method (9) in defining the region of interest (ROI), because the ROI outlined in this standard manner did not represent the actual infarct lesion. For infarct lesions less than the whole MCA territory, the $D_{ischemic}$ value measured in this standard manner should be higher than that from the actual infarct lesion. This may explain a lower NWU and cutoff value than those in the previous study (9). Although the predictive power in this study is not as strong as that in a previous study (9), the current study still provided a feasible method to identify the risk of ME at an early phase of stroke, especially in the primary stroke centers without CTP technique.

It is interesting to note that the current study suggested that there may exist a "time window" for using NWU to predict

**TABLE 4 |** AUC of NWU in different time windows.

| Time window | AUC | *N* |
|---|---|---|
| 0–3 h | 0.649 | 39 |
| 3–6 h | 0.500 | 33 |
| 6–9 h | 0.788 | 17 |
| 9–12 h | 0.958 | 10 |
| 12–15 h | 0.778 | 10 |
| 15–24 h | 1.000 | 10 |

*Time, time from onset to first image; AUC, area under curve.*

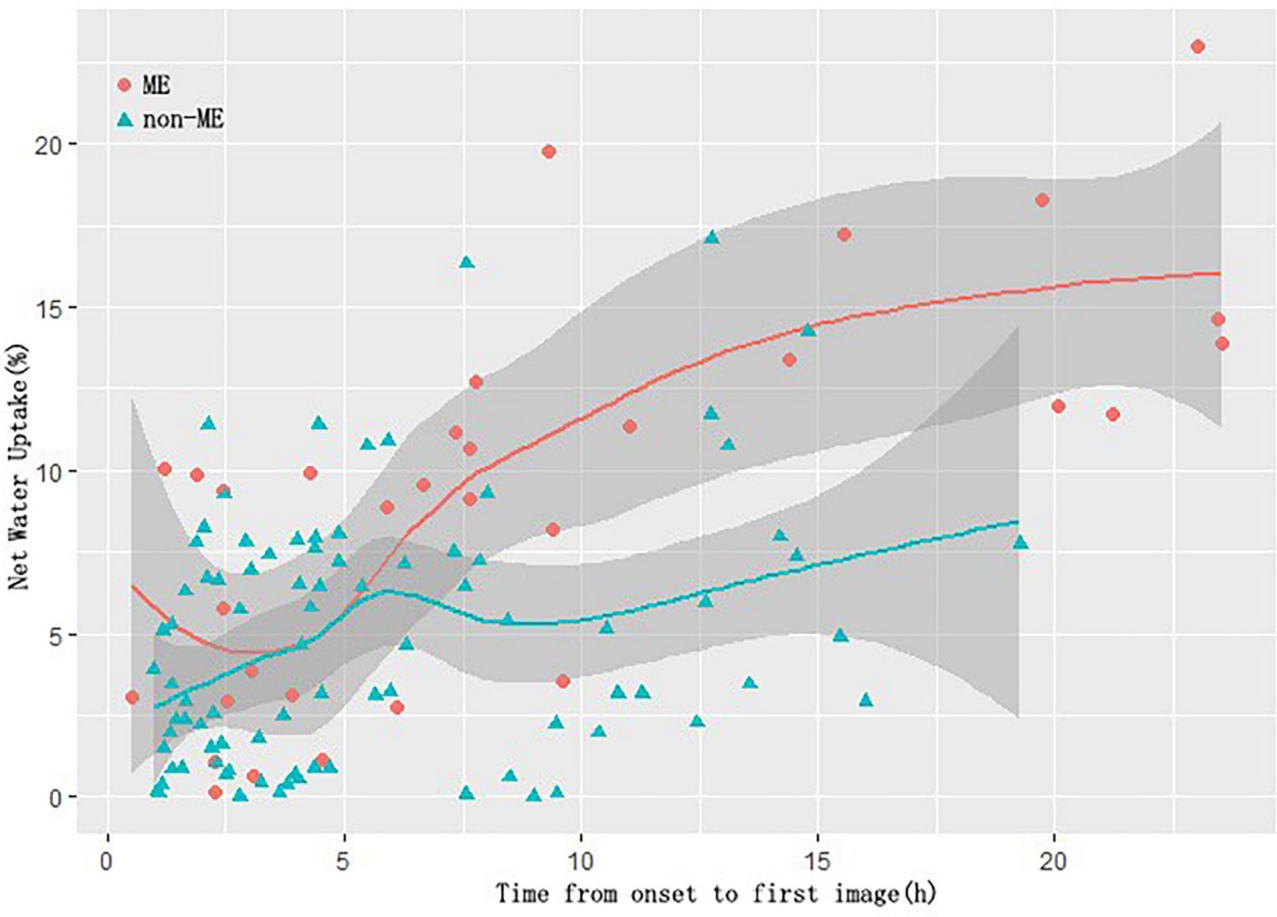


**FIGURE 4 |** Scatterplot of NWU vs. the time from onset to first image.

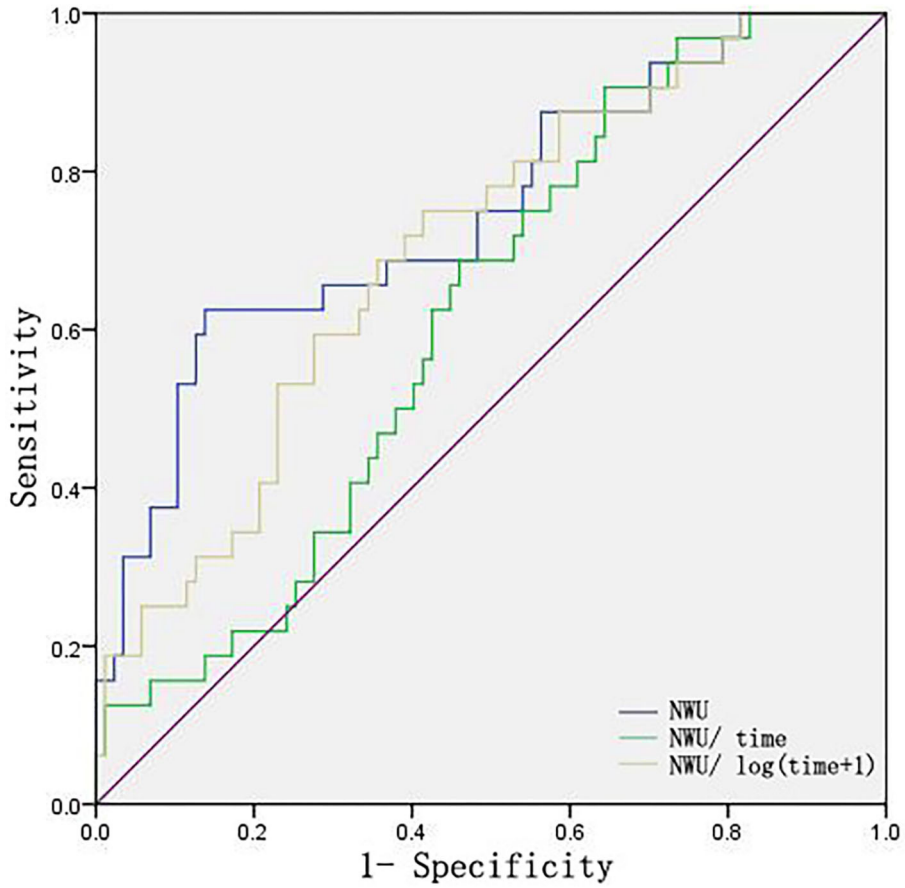


**FIGURE 5 |** ROC curves of NWU, NWU/time, NWU/log (time+1). Time indicates the time from onset to first image.

the development of ME, which has never been reported before. As shown by the AUC of NWU in different time windows (**Table 4**) and the scatterplot of NWU vs. the time from onset to first image (**Figure 4**), when time from onset to first image was within the period from 3 to 6 h, NWU did not perform well in discriminating ME. This phenomenon is very interesting and deserves to be determined in a future prospective study with a larger sample.

Considering the possible effect of the time from onset to first image on NWU, we further compared the prediction power of absolute NWU, NWU/time, and NWU/log (time+1) in the present study. The results showed that NWU and NWU/log (time+1) exhibited greater predictive power than NWU/time. This suggests that the dynamic change of NWU is not in a simple linear relationship with time within 24 h from symptom onset, which is consistent with the view of Pongpat Vorasayan's study (24). However, Broocks' team reported no significant difference among absolute NWU, NWU/time, NWU/log (time+1) in classifying ME within 6 h from symptom onset (9). The discrepancy may be due to the difference in the time from onset to first image (within 6 vs. 24 h) and in the NWU calculation methods (definite infarct lesion vs. blindly outlined MCA territory).

As we know, treatment options such as endovascular treatment and tPA thrombolysis may affect the development of edema (25, 26). To avoid the bias effect of endovascular treatment, patients with mechanical thrombectomy were excluded from this study. Given that the patients with tPA were enrolled in the present study, we further performed multivariable logistic regression analysis by adjusting tPA thrombolysis as a variable to exclude the potential effect of tPA. The results found that tPA thrombolysis did not affect the outcome in the current study.

There are limitations in this study. First, this is a single-center, retrospective study with a small sample size, which makes selection bias hard to avoid. The current method needs to be tested by a multi-center, prospective study with a larger sample size. Second, some data of paramount importance were missed, such as collateral status, infarct volume, dehydration indicators, and long-term follow-up of patients. Third, unbalanced baseline characteristics between two groups may impact the development of ME. To minimize the impact of unbalanced baseline

characteristics, multivariable analysis was performed. Fourth, this standardized and blindly outlined method still requires manual operation. A software that can automatically measure NWU or even combine it with other factors related to ME could be meaningful.

## CONCLUSIONS

NWU calculated in standardized and blindly outlined regions of the MCA territory showed a good prediction power for the development of ME in patients with LHI. The easy method may provide a practical tool to distinguish patients at risk of ME in primary stroke centers with less or no CTP examination, and warrant further testing in the future.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of General Hospital of Northern Theater Command. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

H-BX retrospectively enrolled patients and wrote the paper. Y-FS, NL, J-QW, and G-CC acquired data. H-BX and LT made the figures. B-QY and H-SC analyzed imaging data. H-SC designed the study and critically revised the manuscript. All authors approved the content of the manuscript.

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STUDY PROTOCOL
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# Glibenclamide Advantage in Treating Edema After Intracerebral Hemorrhage (GATE-ICH): Study Protocol for a Multicenter Randomized, Controlled, Assessor-Blinded Trial

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**Introduction:** Brain edema after acute intracerebral hemorrhage (ICH) plays a critical role in the secondary injury of ICH and may heighten the potential for a poor outcome. This trial aims to explore the efficacy of small doses of oral glibenclamide in perihematomal edema (PHE) and the prognosis of patients with ICH.

**Methods and Analysis:** The GATE-ICH trial is a multicenter randomized, controlled, assessor-blinded trial. A total of 220 adult patients with acute primary ICH in 28 study centers in China will be randomized to the glibenclamide group (glibenclamide plus guideline-recommended ICH management) or the control group (guideline-recommended ICH management). Multivariate logistic regression will be used to analyze the relationship between the treatments and primary outcome.

**Study Outcomes:** The primary efficacy outcome is the proportion of poor functional outcomes (modified Rankin Scale $\geq$3) at 90 days after enrollment. The secondary efficacy outcomes include changes in the volume of ICH and PHE between the baseline and follow-up computed tomography scans as well as the clinical scores between the baseline and follow-up assessments.

**Discussion:** The GATE-ICH trial will assess the effects of small doses of oral glibenclamide in reducing the PHE after ICH and improving the 90-day prognosis of patients.

**Clinical Trial Registration:** www.clinicaltrials.gov., NCT03741530. Registered on November 8, 2018.

**Trial Status:** Protocol version: May 6, 2019, Version 5. Recruitment and follow-up of patients is currently ongoing. This trial will be end in the second quarter of 2021.

**Keywords: perihematomal edema, intracerebral hemorrhage, glibenclamide, prognosis, clinical trial**

# INTRODUCTION

Intracerebral hemorrhage (ICH) accounts for 10–15% of the 15 million strokes worldwide each year and has a high mortality and morbidity (1). Compared with Western populations, the incidence of ICH in the Chinese population is higher (1, 2). However, only 12–39% of ICH survivors achieve long-term functional independence (3, 4). Despite the severe outcomes, there are no effective medical or surgical therapeutics available (5).

Perihematomal edema (PHE) after primary ICH, as a combination of early vasogenic edema following cytotoxic edema (6, 7). It is the most critical factor of secondary brain injury that leads to additional neurological deterioration (8, 9). The volume of PHE increases by ∼75% during the first 24 h after ICH. It peaks in ∼5–6 days, and continues for 14 days (1). Managing PHE may be an optimal target for ameliorating secondary brain injury in patients with ICH (10).

Most recently, glibenclamide, a sulfonylurea (SFU) drug and potent inhibitor of the sulfonylurea receptor 1-transient receptor potential melastatin 4 (SUR1-TRPM4) channels, has attracted great interest as a promising therapy for the prevention of cerebral edema after hemispheric infarction. It has been verified in the GAMES-RP study (11–13). Glibenclamide may contribute to mitigating both cytotoxic and vasogenic edema by blocking the SUR1-TRPM4 channels, inhibiting apoptosis, scavenging free radicals, and protecting the integrity of the blood-brain barrier (BBB) (14–16). In patients with ICH with a history of diabetes, SFU used prior to ICH could reduce the accumulation of ICH and PHE volume and improve the short-term prognosis (17, 18). Given the safety and efficacy of oral glibenclamide in treating edema after brain injury, we supposed that the oral formulation of glibenclamide would be efficacious in preventing PHE in patients with acute ICH.

# METHODS AND ANALYSIS

## Study Objectives

The purpose of this hospital-based study is to assess whether small doses of oral glibenclamide would reduce edema and improve the prognosis in patients with ICH.

## Study Design

The Glibenclamide Advantage in Treating Edema after Intracerebral Hemorrhage (GATE-ICH) study is a multicenter, randomized, controlled, assessor-blinded clinical trial. The subjects will be randomized into one of the two intervention arms using a web-based 1:1 centralized randomization process (http://cerebralhemorrhage.applinzi.com. computerized random numbers): (1) the glibenclamide group (glibenclamide plus guideline-recommended ICH management), and (2) the control group (guideline-recommended ICH management). There are four time points of assessment: baseline (t0), 3 days (t1), 7 days (t2), and 90 days (t3) after enrollment (**Table 1**). The **Supplementary File 1** describes the Recommendations of Interventional Trials (SPIRIT), which indicates the recommended items and corresponding page numbers of the present protocol.

**TABLE 1** | Overview of assessment points and measurements.

| Assessment points | Time range |
|---|---|
| t0 | baseline assessment prior to enrollment |
| t1 | 3 days (72 h ± 12 h) post-enrollment |
| t2 | 7 days (168 h ± 12 h) post-enrollment |
| t3 | 90 days (± 7 d) post-enrollment |

## Study Population

The GATE-ICH trial (www.clinicaltrials.gov. NCT03741530) involves 26 hospitals in the Shaanxi Province of China. We will conduct the study based on the recommendations of the Good Clinical Practice guidelines and the Declaration of Helsinki. The trial has been approved by the ethics committee of Xijing Hospital (KY20182067-X-3). The study will include patients with acute primary ICH who have ganglia hemorrhage of 5–30 mL confirmed by a baseline head computed tomography (CT). The inclusion criteria and exclusion criteria are shown in **Box 1**. Potential patients will be identified by emergency physicians and the initial neurologists. Trained neurologists at every center will be requested to make a definite diagnosis of ICH and confirm that each patient has met the inclusion criteria of the study. A written informed consent form of the present study and additional *post-hoc* analysis will be sent to all of the subjects or their guardians by the trained neurologists.

## Randomization

The baseline data of potential participants will be provided to the research coordinators by investigators at every center. Through a web-based 1:1 randomization (computerized random numbers) process (http://cerebralhemorrhage.applinzi.com/index.php), patients will be assigned to one of the two intervention arms by the research coordinators.

## Training of Investigators

To ensure the quality of the GATE-ICH trial, all the investigators from every center are required to receive official training regarding the study protocol, Good Clinical Practice guidelines, clinical scores including the Glasgow Coma Scale (GCS), National Institutes of Health Stroke Scale (NIHSS), ICH score, Barthel index, and modified Rankin Scale (mRS), as well as the recognition of basal ganglia hemorrhage on head CT.

## Trial Interventions

### Intervention Arms

The time course of plasma glibenclamide levels indicates that an oral formulation of 3.5 mg/day at 4 h after administration is equal to an intravenous formulation of a 0.13-mg bolus followed by a dose of 3 mg/day, which has been proved efficacious and safe for treating edema in patients with ischemic stroke (13, 19).

**BOX 1** | Inclusion and exclusion criteria.

**Inclusion criteria**

1. Age 18–70 years with primary ICH.
2. Baseline CT with basal ganglia hemorrhage of 5–30 mL.
3. GCS score ≥ 6.
4. Symptom onset <72 h prior to admission.
5. Informed consent.

**Exclusion criteria**

1. Supratentorial ICH planned to evacuation of a large hematoma.
2. Hemorrhage breaking into ventricles of the brain.
3. Prior significant disability (mRS ≥ 3).
4. Severe renal disease (i.e., renal disorder requiring dialysis) or eGFR <30 ml/min/1.73 $m^2$.
5. Severe liver disorder, or ALT >3 times or bilirubin >2 times upper limit of normal.
6. BG < 3.1 mmol/L at enrollment, or with the history of hypoglycemia.
7. Having acute ST elevation infarction, or decompensated heart failure, or cardiac arrest, or acute coronary syndrome, or known history of acute coronary syndrome, or acute myocardial infarction, or coronary intervention in the past 3 months.
8. Treatment with sulfonylurea in the past 7 days, including glyburide, glyburide plus metformin, glimepiride, repaglinide, glipizide, gliclazide, tolbutamide, and/or glibornuride.
9. Treatment with bosentan in the past 7 days.
10. Having an allergy to sulfa or other sulfonylurea drugs.
11. Known G6PD deficiency.
12. Pregnant women.
13. Breast-feeding women disagreeing to participate the study or to discontinue breastfeeding during and after the study.
14. Being enrolled in another study and receiving an investigational drug.
15. Refusing to be enrolled, having poor compliance, and/or tending to withdraw.

ALT, Alanine aminotransferase; BG, Blood glucose; CT, computed tomography; eGFR, estimated glomerular filtration rate; GCS, Glasgow Coma Scale; G6PD, Glucose-6-phosphate Dehydrogenase; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale.

The half-life of glibenclamide is 4.0–13.4 h in elderly patients and 4.0–13.9 h in younger patients (20). In order to achieve a stable drug concentration that coincides with three mealtimes, we chose a dose of 1.25 mg, 3 times per day (3.75 mg/day). In our pilot study, 10 patients in the glibenclamide group and 12 patients in the control group were enrolled. The plasma concentration of glibenclamide elevated to 47.6 ng/mL at 2 h after the first dose, and gradually achieved by steady state plasma concentration of glibenclamide at 72 h (26.7 ng/mL). Patients assigned to the glibenclamide group will receive tablets containing 1.25 mg of glibenclamide [Yun Peng Pharmaceutical Co., Shanxi, China; each capsule (2.5 mg)] three times daily (no more than 30 min before a meal) for 7 consecutive days after enrollment in addition to the usual care and medications for ICH. Patients in the control group will receive only the usual care and medications for ICH. Glibenclamide tablets should not be administered after head CT on day 7. Treatment with other SFU agents is not permitted during the 90-day follow-up period in either group.

### Patient Safety

The study drug must be reduced to 1.25 mg twice daily if any of the following conditions are present: (1) laboratory-confirmed blood glucose (BG) level <3.1 mmol/L; (2) or three laboratory-confirmed BG levels <3.9 mmol/L within 12 h. The study drug must be discontinued if either of these conditions occur twice. In patients with hyperglycemia during their hospitalization, increasing the dosage of glibenclamide or substituting glibenclamide with other SFU agents is not permitted. In patients with a laboratory-confirmed BG level <3.9 mmol/L, administration of 50% glucose is suggested, according to the following formula: supplementation volume of 50% glucose = [100–laboratory-confirmed BG (mg/dL)] × 0.4 mL. Other highly hyperosmotic glucose solutions with the same amount of sugar are also allowed.

### Medical Care in the Hospital

Both groups in the present study will receive the same background care. Traditional dehydration therapy is not recommended for patients without intracranial hypertension. In patients with intracranial hypertension, the selection of osmotherapy medicines depends on local availability. The use of supplemental fluids is based on the clinical status of the subjects. In patients randomized to the glibenclamide group with inadequate intake, but not meeting the standard nasal feeding, 5 or 10% glucose is recommended to avoid hypoglycemia. The management of blood pressure and all other medical care for ICH patients will adhere to the ICH guidelines (21).

## Study Procedures

**Figure 1** presents the flow chart of the GATE-ICH trial. Based on the inclusion and exclusion criteria, the potential subjects offering informed consent will be randomized. At baseline, demographics, medical history (acute ischemic stroke, ICH, coronary events, diabetes mellitus, and hypertension), physical examination results, clinical scores (NIHSS, GCS, ICH score, Barthel index, mRS), vital signs, and head CT results will be recorded. Routine laboratory tests for patients with ICH will be conducted (routine blood tests, renal and liver function tests, serum lipid, fasting glucose, routine urine tests, electrocardiography, and head CT) on days 1, 3, and 7. Clinical scores (NIHSS, GCS, Barthel index, and mRS) on day 3 and day 7 or the day of hospital discharge will be collected. The Barthel index and mRS on day 90 will be assessed. During the entire period of hospitalization, concomitant treatments, adverse events (AEs), and serious AEs (SAEs) will be documented.

### Imaging Evaluations

A baseline CT evaluation of ICH volume will be performed by the investigators and study coordinators in each center using an image matrix of 512 × 512 with a slice thickness of 5 mm. The three CT assessments of the same subject should use the same type of CT. At an initial meeting, all investigators will be trained on the methodology of hematoma volume calculation using ABC/2 and provided with an electronic instruction manual. CT scans will be performed as standard procedures, and additional magnetic resonance imaging or other scans will be used when

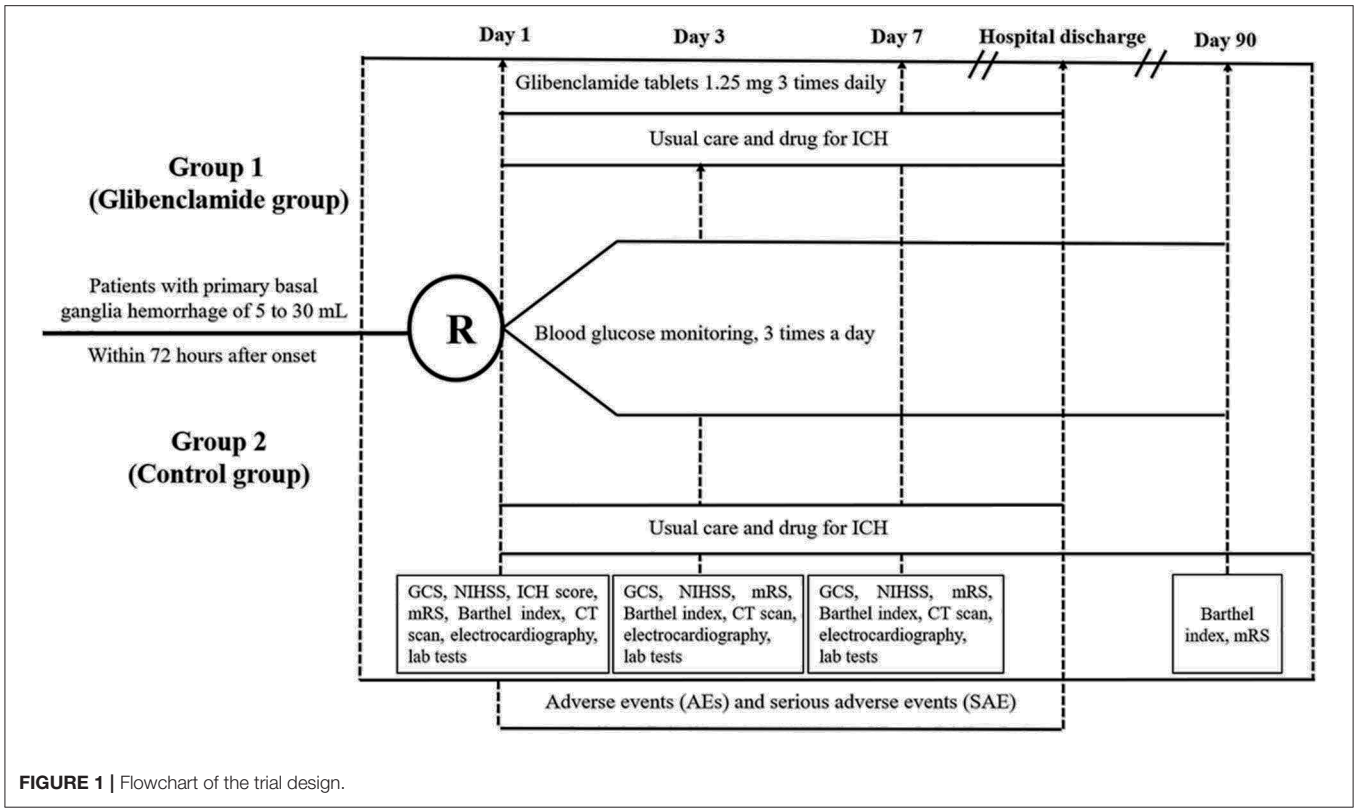


**FIGURE 1 |** Flowchart of the trial design.

patients appear to have neurological deterioration. The final results of the three CT scans in every patient will be evaluated by independent investigators blinded to the clinical variables using the 3D Slicer software package (version 4.10.2; National Institutes of Health, Bethesda, MD, USA). ICH and PHE volumes will be measured using a semiautomatic volumetric algorithm as in a previous study (**Figure 2**) (22, 23).

### BG Monitoring

During the first 7 days after enrollment, BG will be monitored 3 times a day. In patients with hyperglycemia, BG will be monitored at least every 2 h until BG returns to normal.

### Post-discharge Follow-Up

A telephone follow-up after discharge is planned at 90 days after enrollment. Post-discharge follow-up will be performed by the investigators in every center who did not participate in other parts of the trial, including the randomization or treatment of the subjects. When all efforts to follow-up have been made but have failed, the patients will be recorded as lost to follow-up at the end of the case report form.

## Study Outcomes

### Efficacy Outcomes

The primary efficacy endpoint is the percentage of unfavorable outcomes (mRS $\geq$3) at 90 days post-enrollment. The secondary efficacy endpoints include changes in the volume of ICH and PHE between the baseline and follow-up CT scans, and changes in the clinical scores between baseline and follow-up.

### Safety Outcomes

The safety endpoints include the BG-related safety and cardiac-related safety of glibenclamide tablets as follows: (1) hypoglycemia (BG <3.1 mmol/L), (2) symptomatic hypoglycemia (hypoglycemia with confirmed hypoglycemic symptoms), (3) incidence of cardiac AE/SAEs or a QT interval of >500 ms, and (4) incidence of all-cause mortality.

## Blinding

The outcome assessors and data analysts will be blinded to the interventions. There will be one investigator assessing the functional outcomes in every center who will be blinded to the intervention received by the participants. All of the imaging evaluations will be conducted by independent investigators blinded to the clinical variables, interventions, and functional outcomes. The analyses will be conducted by blinded biostatisticians.

## Data Quality

To narrow the gap of uniformity between the centers and ensure the quality of the study, the following guidelines will be implemented: (1) an initial meeting will be held for all of the principal investigators and research coordinators from the participating centers before the commencement of the GATE-ICH study; (2) in each research center, the principal investigator (PI) will administer the trial and the monitor the quality of the data; (3) to ensure the quality of the trial, training sessions, phase meetings, and monthly monitoring visits at every center will be required; and (4) the Quality Control and Assurance Committee

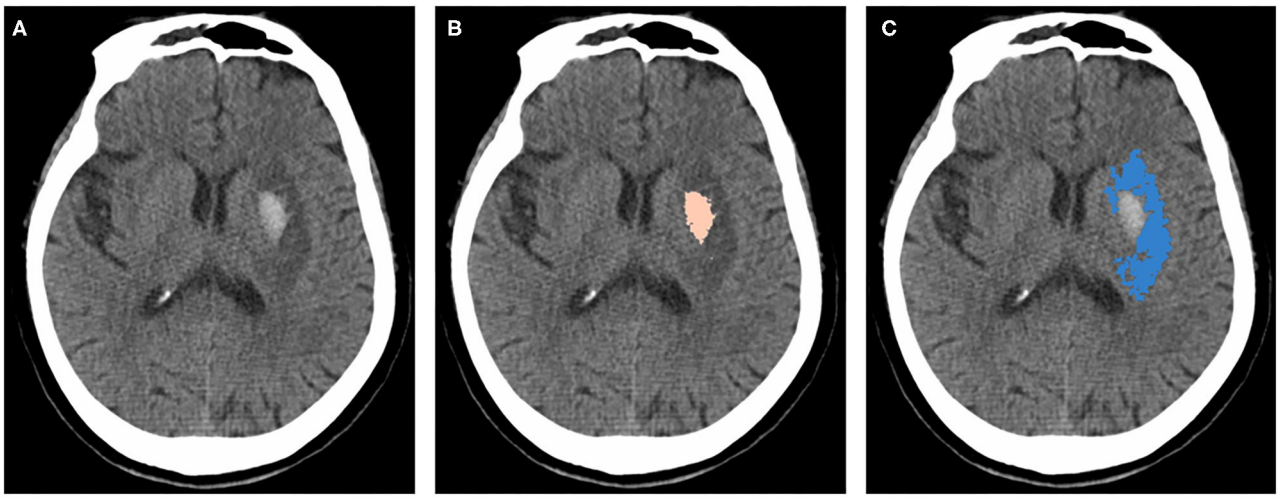


**FIGURE 2 |** Measurements of hematoma and PHE using 3D slicer software package. **(A)** original image of a patient with ICH. **(B)** hematoma marked with pink. **(C)** PHE marked with blue. ICH, intracerebral hemorrhage; PHE, perihematomal edema.

will prepare monthly reports regarding the progress of the trial, including patient recruitment, randomization, protocol adherence, and completeness of the data. The informed consent forms, case report forms, reports of AE/SAE and CT data of Digital Imaging and Communications in Medicine (DICOM) will be securely stored in a locked file cabinet in a secure office. All of the digital data will be stored in a password- and firewall-protected secure computer. The sponsor of the trial will have access to the final data.

## Monitoring

The PI in each center will manage quality control by monitoring the administration of the trial in accordance with the protocol, applicable guidelines, and regulations. Monthly reports regarding the progress of the trial will be prepared by the Quality Control and Assurance Committee, including patient recruitment, randomization, protocol adherence, reports of AE/SAE and completeness of the data. All participating sites will have phase meetings and monthly monitoring visits to verify consent, eligibility criteria, anomalous data, and reported SAEs.

## Determination of the Sample Size

The sample size was set at 220 to provide at least 80% power (1-β) to detect an 23.3% absolute risk reduction in the primary efficacy outcome for patients in the glibenclamide group compared to those in the control group, using a test of two-sided significance with a 5% type I error (α). The rate of non-adherence to the treatment protocol and overall loss to follow-up is assumed to be 15%. In our pilot study, the volume of PHE in patients receiving glibenclamide was significantly smaller than control group at day 7 (21.74 ± 9.70 mL vs. 31.22 ± 10.16 mL, $p = 0.038$). At 90 days, 33.3% of patients in control group had unfavorable outcomes while the data was 10.0% for the patients assigned to glibenclamide group (**Supplementary File 2**).

## Statistical Considerations

Patients in our study will be analyzed according to the intention-to-treat principle. Analyses will be conducted by blinded biostatisticians. Baseline data will be analyzed using univariate analyses. Categorical variables will be presented as rates, whereas continuous variables will be expressed as median (interquartile range) or mean ± standard deviation. The primary and secondary outcomes will be compared between patients randomized to the glibenclamide group and the control group using the Chi-square test or Fisher's exact-test and the Student's *t*-test or Wilcoxon rank-sum-test. Logistic multivariate analyses will be used to adjust for potential confounding effects of different variables and estimate the adjusted odds ratios and associated 95% confidence intervals. Two-sided $p$-values $< 0.05$ in all tests will be considered significant. The statistical analysis will be performed with SPSS version 19.0 software (SPSS Inc., Chicago, IL, USA).

## Patient and Public Involvement

Patients were not involved in the design of the study. The burden of intervention and the participation time in the research will not be assessed by the patients themselves. During the treatment stage, analysis of adverse reactions (such as symptoms of low blood sugar) will require timely feedback from the patients, assessment of the investigators, and confirmation by assessment instruments. At the termination of the trial, a scientific article will be authored to present the main results, and a brief summary of the results in plain language will be provided to all participants.

## Protocol Amendments

Any amendments to the protocol will be requested with the agreement of the GATE-ICH Study Group, Sponsor, and Funding Body. Following approval by the ethics committee, the modifications to the protocol will be communicated to the

trial investigators and the trial registry (and if required, to the trial participants).

## DISCUSSION

The GATE-ICH trial is a multicenter, randomized, controlled, assessor-blinded clinical trial in China. We will assess the hypothesis that small doses of oral glibenclamide is an effective method to reduce the PHE after ICH and to improve the 90-day prognosis of patients. The trial will provide new evidence regarding the management of PHE in patients with ICH.

In patients with supratentorial ICH, the hematoma volume was one of the important factors predicting outcomes (1). Patients with massive ICH (volume >30 mL) were associated with an increased risk of poor outcomes, and might respond better to surgical treatment rather than conservative treatment (24, 25). In addition, the clinical outcomes were not influenced by the PHE in patients with hematoma volume >30 mL no matter the location (10, 26). Results of previous studies found that the effect of PHE on 90-day unfavorable outcome was more relevant in patients with hematoma volume <30 mL than those with massive ICH (26–29). In patients with hematoma volume <30 mL, there was a significant association between PHE and poor outcome in basal ganglia ICH (10, 26). However, the relationship of PHE and poor outcome was controversial in lobar ICH (10, 26). Thus, basal ganglia hematomas with volumes <30 mL could be regard as an optimal target for interventions designed to ameliorate PHE after ICH (10).

Although the conservative treatment was usually suggested in patients with hematoma volume <30 mL, there are few effective therapies available for treatment of PHE after ICH (25). Traditional dehydration therapy is the most common option in clinical practice; however, its' effect is modest (7, 30). Identifying anti-edema drugs may be a promising intervention for ICH. As a candidate anti-edema drug, glibenclamide has been proven effective for the treatment of brain swelling after large hemispheric infarction in humans (12). In the GAMES-Pilot study, vasogenic edema appears to be reduced in patients with acute ischemic stroke treated with glibenclamide (16). It has been verified that glibenclamide could improve the injury of ICH through its' anti-inflammatory effects and scavenging of free radicals in pre-clinical studies (14, 15). Our study aims to test the efficacy of glibenclamide for treating edema and improving 90-day outcomes after ICH in a treated group compared to a control group in human subjects.

The GATE-ICH study is a multicenter randomized, controlled, assessor-blinded trial. Some limitations of this trial should also be noted. First, as a definite limitation in this trial, the placebo control was originally designed at the beginning of the design phase. However, unexpected failure of the placebo production line forced us to adjust initial study protocol from the placebo control to the blank control. After rigorous evaluation, the main outcome was a subjective outcome indicator and might be biased by the placebo effect, while both of imaging outcomes and safety outcomes were objective outcomes with limited placebo effect. In order to avoid the influence of placebo effect as much as possible, the outcomes evaluation and statistical analysis would be blindly processed by independent researchers throughout the study. Second, some background treatments were not standardized. For example, the selection of osmotherapy medicines depended on local availability in patients with intracranial hypertension. Thus, background treatments should be standardized as much as possible in future studies. Last but not least, the population was limited to the Chinese patients, which might restrain generalizability of the results to other populations. Thus, multicenter research in more countries will be needed.

### Trial Status

We conceived and designed the present trial in 2018. The trial was registered on November 8, 2018 (ClinicalTrials.gov, NCT03741530) and initiated on November 25, 2018. The protocol was version 5 on May 6, 2019. At the time this manuscript is being submitted, the enrollment and follow-up of patients is currently ongoing. This trial will be end in the second quarter of 2021.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of Xijing Hospital. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

This trial was conceived by FY and WJ. WJ is the chief investigator. JZ is a sub-investigator. CS assists with the study and analysis. LL, XY, XW, LY, JG, KW, and FF are the principal investigators and consulting clinicians at each study site. The first version of the manuscript was produced by JZ and FY with advice from WJ. All authors are responsible for the designation and conduction of this study as well as the data analysis, the drafting, and the reviewing of the final content of the paper.

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## SUPPLEMENTARY MATERIAL

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# Computed Tomography Based Score of Early Ischemic Changes Predicts Malignant Infarction

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**Background and Purpose:** Identification of ischemic stroke patients at high risk of developing life-threatening malignant infarction at an early stage is critical to consider more rigorous monitoring and further therapeutic measures. We hypothesized that a score consisting of simple measurements of visually evident ischemic changes in non-enhanced CT (NEMMI score) predicts malignant middle cerebral artery (MCA) infarctions (MMI) with similar diagnostic power compared to other baseline clinical and imaging parameters.

**Methods:** One hundred and nine patients with acute proximal MCA occlusion were included. Fifteen (13.8%) patients developed MMI. NEMMI score was defined using the sum of the maximum diameter (anterior-posterior plus medio-lateral) of the hypoattenuated lesion in baseline-CT multiplied by a hypoattenuation factor (3-point visual grading in non-enhanced CT, no/subtle/clear hypoattenuation = 1/2/3). Receiver operating characteristic (ROC) curve analysis and multivariable logistic regression analysis were used to calculate the predictive values of the NEMMI score, baseline clinical and other imaging parameters.

**Results:** The median NEMMI score at baseline was 13.6 (IQR: 11.6–31.1) for MMI patients, and 7.7 (IQR: 3.9–11.2) for patients with non-malignant infarctions ($p < 0.0001$). Based on ROC curve analysis, a NEMMI score >10.5 identified MMI with good discriminative power (AUC: 0.84, sensitivity/specificity: 93.3/70.7%), which was higher compared to age (AUC: 0.76), NIHSS (AUC: 0.61), or ischemic core volume (AUC: 0.80). In multivariable logistic regression analysis, NEMMI score was significantly and independently associated with MMI (OR: 1.33, 95%CI: 1.13–1.56, $p < 0.001$), adjusted for recanalization status.

**Conclusion:** The NEMMI score is a quick and simple rating tool of early ischemic changes on CT and could serve as an important surrogate marker for developing malignant edema. Its diagnostic accuracy was similar to CTP and clinical parameters.

**Keywords: stroke, brain herniation, biomarkers, computerized tomography, malignant infarction, edema quantification**

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## BACKGROUND

Stroke due to large vessel occlusion (LVO) is one of the major global causes of disability and death (1). Although endovascular thrombectomy has significantly improved clinical outcome, in particular after middle cerebral artery (MCA) occlusion, some patients nevertheless develop progressive cerebral edema with mass effect and transtentorial herniation, defined as malignant middle cerebral artery infarction (MMI) (2, 3). Rapid identification of patients at risk of life-threatening edema is important at an early stage of the clinical workflow in order to consider more rigorous monitoring of patients and, ultimately, triage for decompressive hemicraniectomy (4). A recent meta-analysis of multiple randomized trials for decompressive hemicraniectomy in LVO stroke with a total of 338 patients demonstrated a significant reduction of mortality after decompressive surgery by 39% compared to best medical treatment, and an increase in the number of patients with only mild to moderate disability (modified Rankin scale 2–3) by 13% (5). Cerebral edema due to ischemic stroke is considered to reach its maximum extent within 2–5 days after the initial vessel occlusion (4). In the case of malignant infarction, this usually comes with severe clinical deterioration. With high probability of already manifest brain tissue damage secondary to increased intracranial pressure at time of herniation, patients at risk of MMI should be identified at an earlier timepoint in order to benefit as much as possible from invasive therapy (6, 7). Clinical independent predictors of MMI have been widely discussed in the literature and include elevated levels on the National Institute of Health Stroke Scale (NIHSS), history of arterial hypertension, female sex, congestive heart failure and younger age (8–11). Radiological predictors include a lower ASPECTS with hypodense ischemic changes on non-enhanced CT (NECT) secondary to increased net water uptake (NWU) (12–14). Nevertheless, these areas of hypodensity in NECT are often subtle and depend on time passed since stroke onset and other factors, in particular the presence of intracranial collaterals and core infarct volume (15). CT Perfusion (CTP) with measurement of CBV and permeability may further facilitate early detection of malignant edema, but requires multimodal imaging (13, 16, 17). In addition, higher clot burden, more proximal thrombus location, and poor intracranial collaterals have been described as predictors for MMI in CT-angiography (13). Yet, simple and widely feasible approaches to predict MMI at an early stage are sparse.

We hypothesized, that in patients with acute LVO, a scoring system based on simple measurement of the maximum anterior-posterior and mediolateral diameter of hypodense ischemic changes (AP+ML) in admission NECT, multiplied by a visually rated hypoattenuation factor of the hypodense lesion is associated with MMI (NEMMI score). The aim of this study was to assess the diagnostic ability of the NEMMI score in comparison to other common predictors of a malignant course after LVO. For this purpose, performance of the NEMMI score was tested against CTP-derived core lesion volume, and baseline clinical parameters.

## MATERIALS AND METHODS

### Patients

Ischemic stroke patients with LVO of the MCA territory admitted between January 2014 and July 2016 at the University Medical Center Hamburg-Eppendorf, Germany ($n = 109$ patients) were retrospectively screened. As only anonymized data were registered, no informed consent was necessary in accordance with the ethical review board approval from the Ethics Committee of the Hamburg Chamber of Physicians (Hamburg, Germany).

The data on which the findings of this study are based are available from the corresponding author on reasonable request.

Patient inclusion criteria for this study were as follows: (1) Acute ischemic MCA stroke secondary to LVO confirmed by multimodal CT within 6 h from symptom onset (non-enhanced CT [NECT], CT angiography, and CT perfusion [CTP]); (2) Visually evident early infarct lesion with hypoattenuation in admission NECT and/or lesion in CTP with reduced cerebral blood volume; (3) Follow-up CT 24–48 h after symptom onset; (4) Documented NIHSS score on admission; (5) Absence of intracranial hemorrhage and/or presence of old infarct lesions in admission NECT. Baseline and follow-up clinical characteristics and demographic information were extracted from the medical records, including use of mechanical recanalization and/or need for decompressive hemicraniectomy.

### Definition of Malignant Infarction

Presence of malignant middle cerebral artery infarction (MMI) was defined as space-occupying infarct (>1/2 affected MCA territory) in follow-up CT at 24–48 h after admission with neurological signs of transtentorial/subfalcine herniation requiring decompressive hemicraniectomy or subsequent death secondary to edematous mass effect (12, 17, 18).

### Imaging

Patients received a multimodal stroke imaging protocol at admission with NECT, CT angiography and CTP on an iCT 256 (Philips Healthcare, Best, the Netherlands) or SOMATOM force (Siemens Healthcare, Erlangen, Germany) scanner. NECT: Collimation 64 × 0.6 (force: 96 × 0.6), pitch 0.297 (force: 0.55), rotation time 0.4 s (force: 1), field of view 270 mm, tube voltage 120 kV (force: 100), tube current 300 mA (force: 406), 4.0 mm slice reconstruction. CT angiography: Pitch 0.985 (force: 0.35), rotation time 0.4 s (force: 0.25), field of view 220 mm, tube voltage 120 kV (force: 70–120), 300 mAs (force: 117–200), 2.0 mm slice reconstruction, 5 mm maximum intensity projection reconstruction with 1 mm increment. CTP: Rotation time 0.5 s (force: 0.5), field of view 220 mm, tube voltage 80 kV (force: 70), tube current 140 mAs (force: 170), 5 mm slice reconstruction, slice sampling rate 1.8 s (force 1.5), biphasic injection with 40 mL of highly iodinated contrast medium with 400 (mmol/L)/mL injected with 6 mL/s followed by 40 mL saline chaser bolus. Imaging data sets were assessed for quality with exclusion in case of severe motion artifacts. Raw perfusion data were analyzed on a Siemens workstation using Syngo VPCT Neuro software (Siemens Healthcare, Erlangen, Germany) or on

a Philips workstation using IntelliSpace Portal software (Philips Healthcare, Best, the Netherlands).

## Assessment of NEMMI Score

Ratings were performed retrospectively on NECT images acquired not later than 6 h after symptom onset by two experienced radiologists (>5 years clinical practice). The raters were blinded to specific patient data (i.e., age, subsequent evolution of malignant infarction). Scans with early hypoattenuated infarct lesions were than selected for assessment of the NEMMI score. The ratings were assessed for interrater reliability. Subsequently, a consensus reading of the

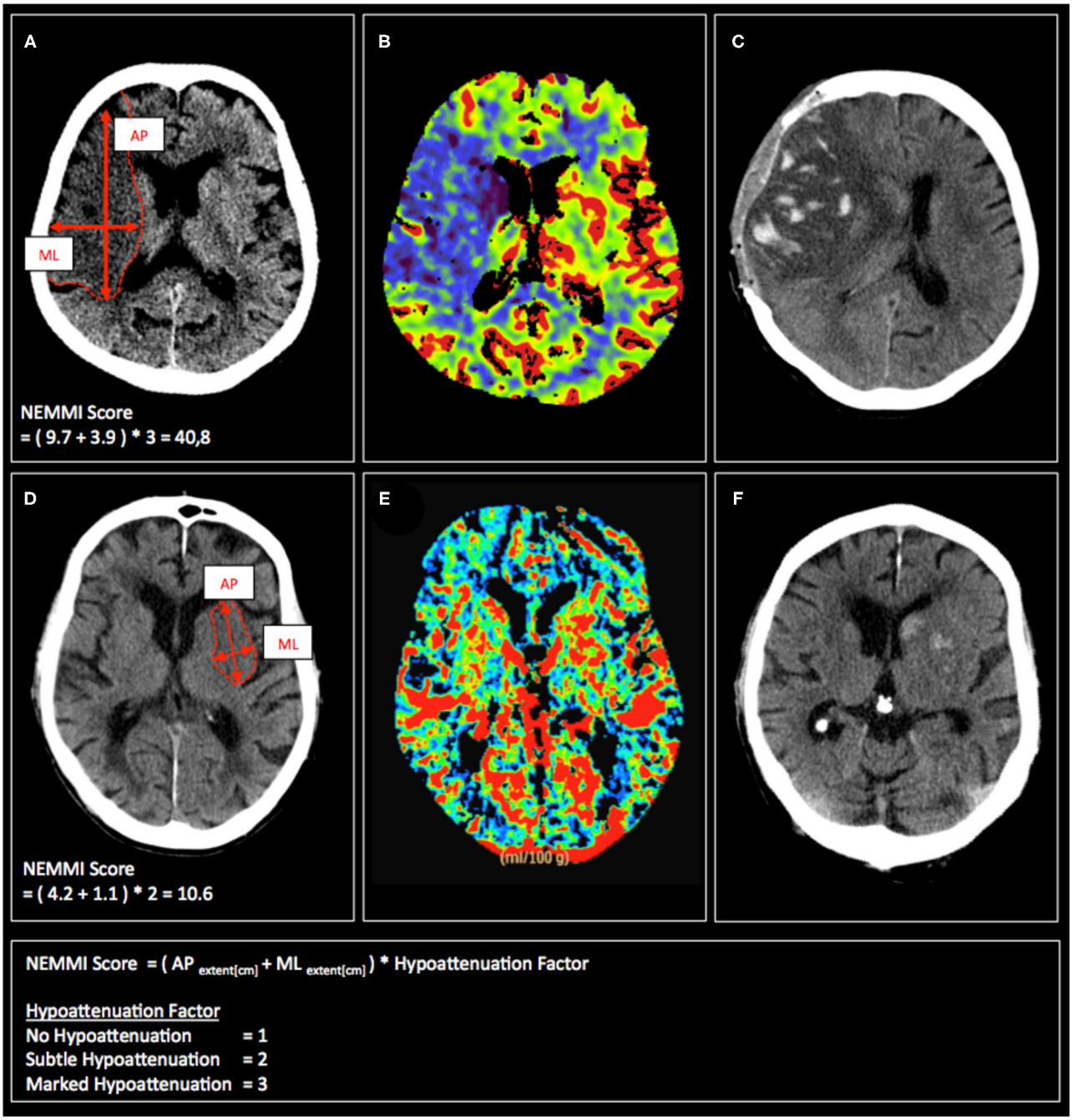


**FIGURE 1 |** Exemplary admission CT scans **(A,D)**, CBV maps **(B,E)**, and follow-up CT scans **(C,F)** of patients with acute MCA occlusion, who subsequently develop malignant infarction (upper row) or have a non-malignant clinical course (lower row). Calculation of the respective NEMMI scores as the sum of the maximum AP and ML early lesion diameter multiplicated by the visual hypoattenuation factor is depicted in **(A,D)**.

cases was performed and only consensus measurements used for analyses.

The assessment of the NEMMI score was conducted in the following way: In the axial slice with the most prominent hypoattenuation, the maximal anterior-posterior (AP) and medio-lateral (ML) extension of the early lesion was measured in centimeters [cm] with the measurement tool provided by the image viewer of the hospital radiological information system (Centricity RIS-i 6.0, General Electric, Boston, MA, USA). In order to take into account varying hypoattenuation of the core lesion, the sum of the maximum lesion dimension (AP+ML [cm]) was then multiplied by a hypoattenuation factor of the hypodense lesion (3-point visual estimate of the hypodensity: No hypodensity = 1; Subtle hypodensity = 2; Clearly demarcated hypodensity = 3; **Figure 1**). In order to validate the visually assessed hypoattenuation factor, the gold standard of net water uptake (NWU) was assessed through a standardized image post-processing protocol according to Broocks et al. (12) and compared to the initially rated hypoattenuation factor (**Figure 2**).

## Statistical Analysis

Absolute and relative frequencies for all patient characteristics were determined, separately for patients with and without MMI. A *t*-test was performed to compare ordinal data with normal distribution, while a Mann–Whitney *U*-test was used otherwise. A *p*-value of $<0.05$ was regarded as statistically significant. Medians are illustrated with the respective interquartile ranges (IQR), means with the respective standard deviation (SD).

The Spearman's rank correlation coefficient was measured to assess the correlation between the visually rated hypoattenuation factor and the conventionally quantified NWU.

The NEMMI score was compared with the most relevant alternative clinical and imaging variables to predict MMI (admission NIHSS score, age, CTP core lesion volume, and recanalization status). Ischemic core volume was defined using absolute cerebral blood volume (CBV) with a threshold at $2.0\,\text{ml} \times 100\ \text{g}^{-1}$, as described by Wintermark et al. (19). Univariable receiver operating characteristic (ROC) curves with the corresponding area under the curve (AUC) were determined

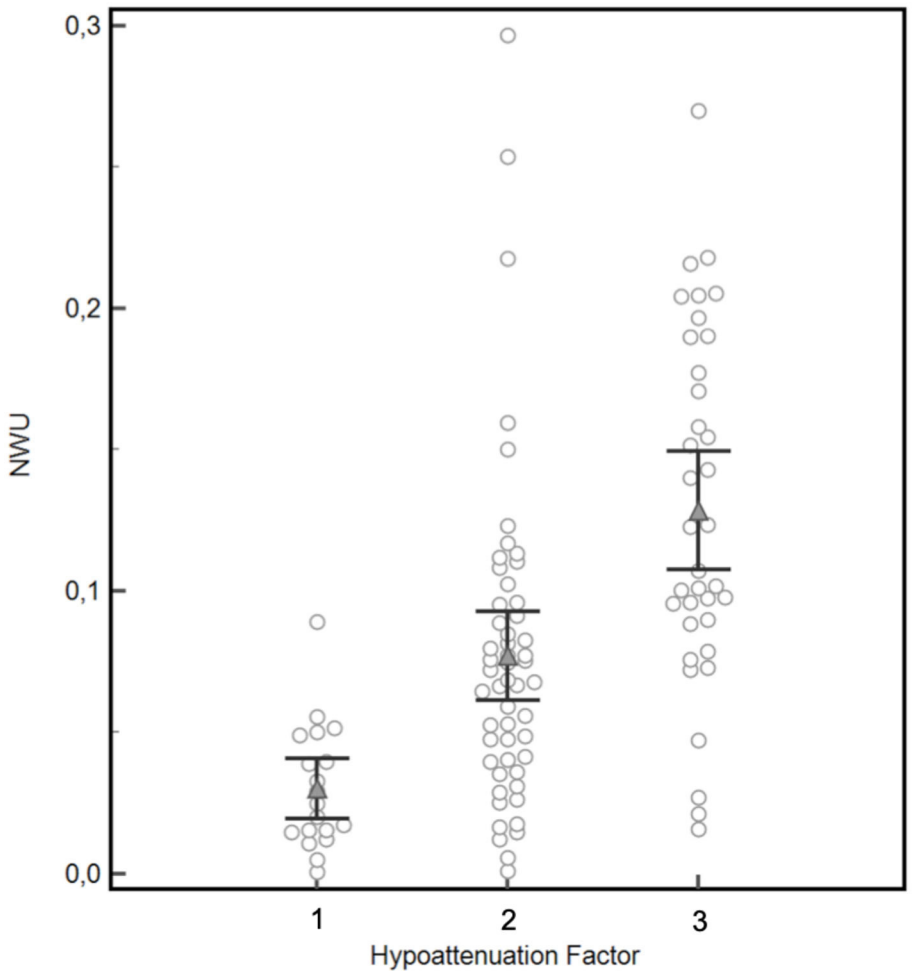


**FIGURE 2 |** Validation of the visually rated hypoattenuation factor by semi-automatic quantification of net water uptake (NWU). Mean NWU differed significantly between the three patients groups classified for hypoattenuation factor 1 (mean NWU 3.0%), 2 (mean NWU 7.7%), and 3 (mean NWU 12.9%), black brackets indicate 95%CI, $p = 0.0001$ for factor 1 vs. factor 2, $p < 0.0001$ for factor 2 vs. factor 3.

to compare the ability of NEMMI and alternative variables at admission to discriminate between patients with MMI and non-malignant MCA territory infarctions. Inter-rater agreement was quantified using intra-class correlation coefficients (ICC).

In order to investigate the independent multivariable contribution of NEMMI and other variables to predict MMI, multivariable logistic regression analyses were performed presenting odds ratio (OR) estimates along with 95% confidence intervals using backwards selection of the independent variables (age, NIHSS, time from onset to imaging, baseline ischemic core volume, NEMMI, and recanalization status).

The open-source statistical software R (The R Foundation) was used for statistical analysis, and the R package ggplot2 for visualization. Receiver operating characteristic analyses were calculated with MedCalc version 12.7 (MedCalc Software, Ostend, Belgium).

## RESULTS

A total of 109 patients fulfilled the inclusion criteria. Of these, 94 (86.2%) had a non-malignant course of disease, while 15 (13.8%) suffered from MMI with mass herniation. Patient characteristics are depicted in **Table 1**. Median NIHSS on admission (Non-MMI 16 [IQR 12–19]; MMI: 17 [IQR 16–18]; $p = 0.158$) and mean time from symptom onset to hospital admission (Non-MMI 3.3 h [SD 1.8]; MMI: 2.6 [SD 1]; $p = 0.165$) were similar in both groups. Ischemic core volumes showed high variations in non-MMI and MMI patients, with a mean volume of 16.9 mL (SD 17.6) and 50.1 mL (SD 37.7; $p < 0.005$), respectively. Follow-up infarct volume up to 48 h after admission was significantly elevated in patients with malignant clinical course (204.3 mL [SD 57.1] vs. 48.6 mL [SD 51.3]; $p < 0.00001$). The majority of patients in both groups received intravenous lysis (77.6 and 73.3%; $p = 0.715$). Endovascular thrombectomy was more frequent in the non-malignant group (96.8 vs. 73.3%; $p < 0.0007$), with also significant higher proportion of successful mechanical recanalization (TICI 2b/3: 68.1 vs. 18.2%; $p < 0.002$).

**TABLE 1 |** Patient characteristics stratified by malignant and non-malignant infarcts.

| Patient characteristics | Non-malignant | Malignant |
|---|---|---|
| Subjects, *n* (%) | 94 (86.2) | 15 (13.8) |
| Age in years, mean (SD) | 68.6 (14.8) | 56.4 (12) |
| Female sex, *n* (%) | 48 (51.1) | 6 (40) |
| Admission NIHSS, median (IQR) | 16 (12–19) | 17 (16–18) |
| Time from onset to admission, mean h (SD) | 3.3 (1.8) | 2.6 (1) |
| Volume of early infarct (core volume), mean mL (SD) | 16.9 (17.6) | 50.1 (37.7) |
| Follow-up infarct volume, mean mL (SD) | 48.6 (51.3) | 204.3 (57.1) |
| Intravenous lysis, *n* (%) | 73 (77.6) | 11 (73.3) |
| Endovascular thrombectomy, *n* (%) | 91 (96.8) | 11 (73.3) |
| If thrombectomy performed: TICI 2b/3, *n* (%) | 62 (68.1) | 2 (18.2) |
| Anterior-posterior (AP) diameter of early lesion, median cm (IQR) | 3.1 (1.8–4) | 3.9 (3.1–6.3) |
| Mediolateral (ML) diameter of early lesion, median cm (IQR) | 1.6 (1–2) | 2.3 (1.8–3.7) |
| Hypoattenuation factor, median (IQR) | 2 (1–2) | 3 (2–3) |
| NEMMI score, median (IQR) | 7.7 (3.9–11.2) | 13.6 (11.6–31.1) |

*NIHSS, National Institute of Health Stroke Scale; SD, standard deviation; IQR, interquartile range; TICI, thrombolysis in cerebral infarction; NEMMI, non-enhanced malignant media infarction.*

Inter-rater agreement was tested separately for the hypoattenuation factor, and both diameters (AP and ML). The intraclass correlation coefficient showing the reliability of averages of $\kappa$ ratings was 0.88 (95%CI: 0.78–0.93) for the hypoattenuation factor, and 0.91 (95%CI: 0.84–0.95)/0.88 (95%CI: 0.79–0.94) for the AP and ML diameter, respectively.

Measurement of the median maximum lesion diameter on admission NECT was similar in both groups (AP: Non-MMI 3.1 cm [IQR 1.8–4]; MMI 3.9 cm [IQR 3.1–6.3]; $p = 0.144$/ML: Non-MMI 1.6 cm [IQR 1–2]; MMI 2.3 cm [IQR 1.8–3.7]; $p = 0.082$).

Mean NWU differed significantly between the three patients groups classified for hypoattenuation factor 1 (mean NWU 3.0%), 2 (mean NWU 7.7%), and 3 (mean NWU 12.9%), $p = 0.0001$ for factor 1 vs. factor 2, $p < 0.0001$ for factor 2 vs. factor 3 (**Figure 2**). Accordingly, a significant positive correlation was demonstrated for a visually assessed elevated hypoattenuation factor and increased NWU (Spearmans rho = 0.6, $p < 0.0001$, 95%CI of rho: 0.50–0.71).

The median NEMMI score was significantly elevated in patients developing subsequent MMI during their clinical course (7.7 [IQR 3.9–11.2] vs. 13.6 [IQR 11.6–31.1]; $p < 0.0001$; **Figure 3**).

Based on univariable ROC curve analysis, a NEMMI score >10.5 identified MMI with high discriminative power (AUC: 0.84; sensitivity: 93.3%; specificity: 70.7%; Youden J: 0.64), which was higher compared to age (AUC: 0.76), NIHSS (AUC: 0.61), or core lesion volume (AUC: 0.80; **Figure 4**).

In multivariable logistic regression analysis, NEMMI score was significantly associated with MMI (odds ratio: 1.33; 95%CI: 1.13–1.56; $p < 0.001$). Further independent variables that were significantly associated with MMI were recanalization status (OR: 0.04; 95%CI: 0.003–0.39; $p = 0.006$), and time from onset to imaging (OR: 0.22; 95%CI: 0.06–0.78; $p = 0.02$; see **Table 2**). A logistic regression model consisting of the NEMMI score and recanalization showed the highest diagnostic power to predict MMI (AUC: 0.92; 95%CI: 0.85–0.96), equivalent to the model NEMMI score + age + recanalization (AUC 0.92; 95%CI 0.86–0.97), and compared to the clinical models NIHSS + age + recanalization (AUC 0.89; 95%CI 0.81–0.94), NIHSS + recanalization (AUC 0.84; 95%CI 0.76–0.9), NIHSS + age (AUC 0.78; 95% CI 0.69–0.85), and core lesion volume (AUC 0.80; 95% CI 0.72–0.87; **Figure 5**).

## DISCUSSION

Early triage of patients at high risk of malignant infarction for decompressive hemicraniectomy is a clinical challenge

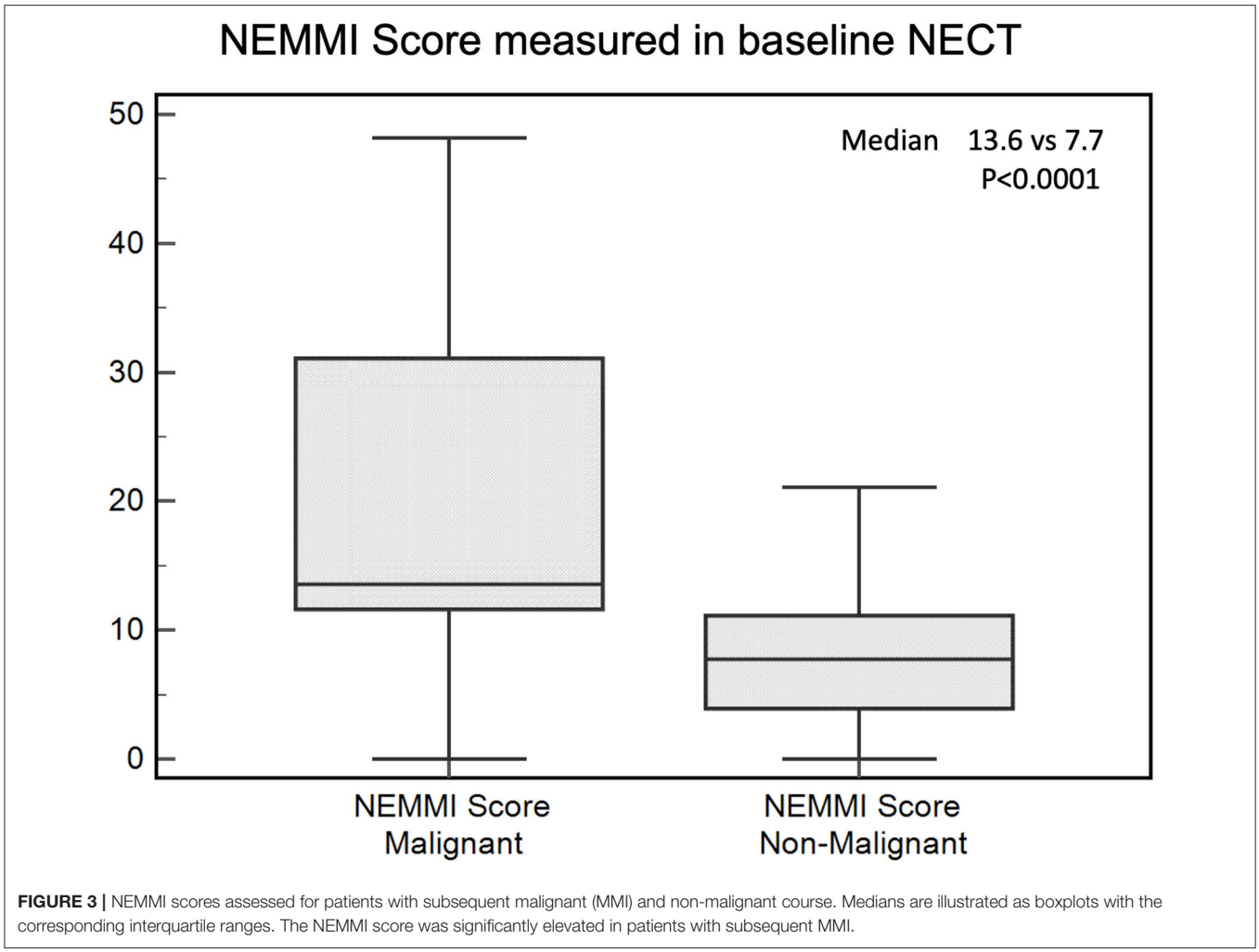


**FIGURE 3 |** NEMMI scores assessed for patients with subsequent malignant (MMI) and non-malignant course. Medians are illustrated as boxplots with the corresponding interquartile ranges. The NEMMI score was significantly elevated in patients with subsequent MMI.

and commonly subject of interdisciplinary discussion. The major predicament is to either wait until neurological deterioration paralleled by radiological findings of mass effect and therefore secondary tissue damage are present or to intervene preemptively with the associated risks of an invasive, potentially non-justified treatment and hence secondary worse outcome. Our study demonstrates the high predictive value of the NEMMI score in admission NECT to identify patients at risk of subsequent malignant infarction with clinical deterioration, need of decompressive craniectomy or letal outcome secondary to mass effect of the edematous tissue.

Other studies suggested accurate prediction of MMI on the basis of multimodal stroke imaging at admission (12, 17, 20, 21). However, these prediction models rely on parameters retrieved from image post-processing. Although this can be achieved semi-automatically, the process is still time consuming, i.e., requires mostly manual segmentation of the cerebrospinal fluid compartment and CBV lesion volume, or quantification of parenchymal net water uptake (12, 17, 22). The latter was demonstrated to be highly associated with a malignant course, but quick assessment is not feasible as it requires calculation of mean densities. An alternative MMI risk prediction model is the EDEMA (Enhanced Detection of Edema in Malignant Anterior Circulation Stroke) score, which is based on clinical and imaging variables within the first 24 h after stroke onset and has recently been externally validated in a Chinese patient cohort (20, 21). Nevertheless, the score cannot be assessed upon admission, as it incorporates features only available after admission CT, i.e., reperfusion therapy, blood glucose and presence of midline shift within 1 day after symptom onset. In contrast, the assessment of the NEMMI score is based on simple measurement of the early lesion extent and visual quantification of the lesion hypodensity in one axial slice of the initial NECT. This can be achieved bedside in the emergency department with conventional radiological image viewers, without the necessity of obtaining additional clinical and laboratory parameters.

This allows consideration of a potential surgical decompressive treatment at the same time as other critical decisions are made by the treating physicians, in particular triage for mechanical thrombectomy or intravenous lysis.

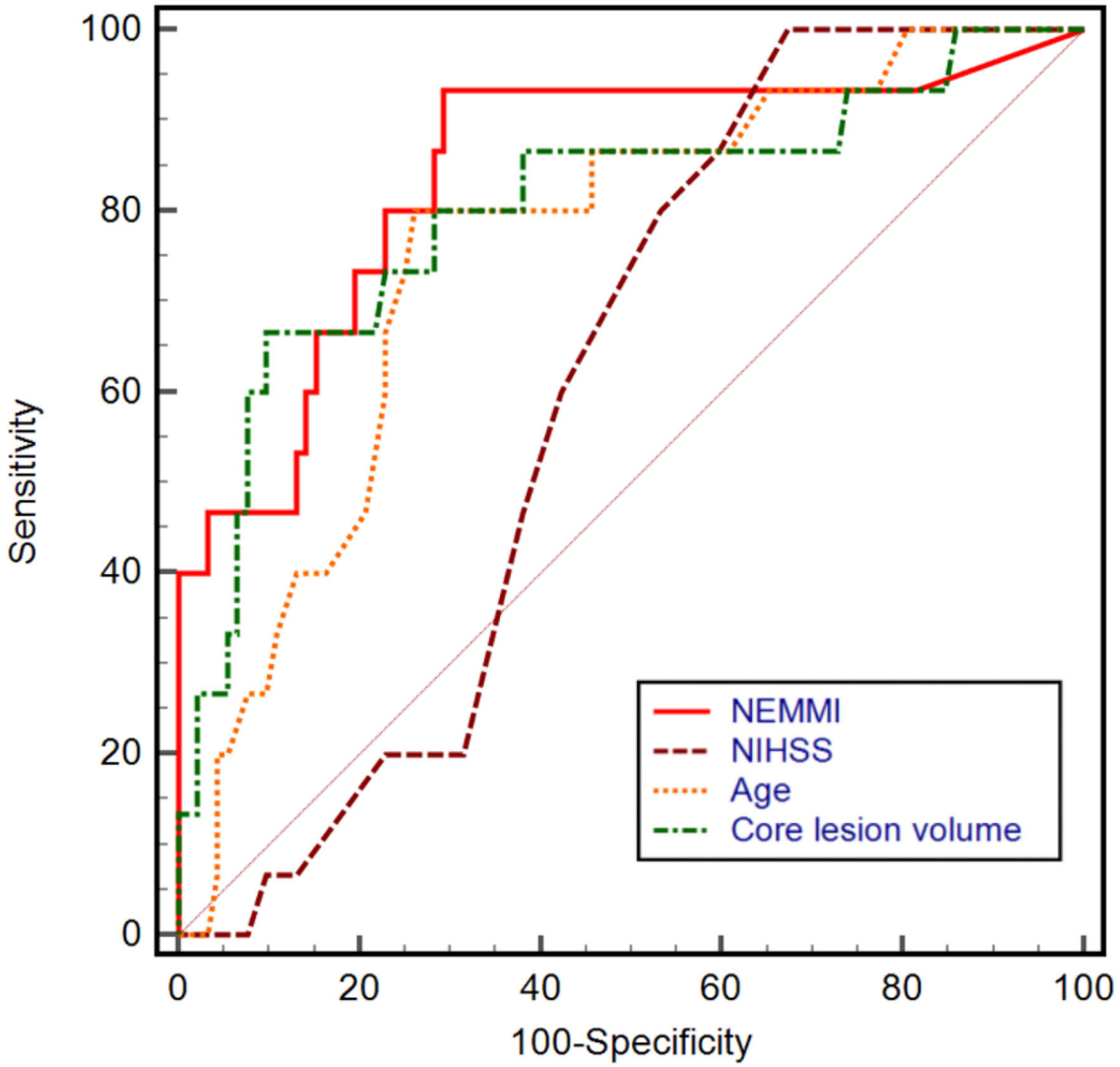


**FIGURE 4 |** Univariable receiver operating characteristic (ROC) curves with the corresponding area under the curve (AUC) of NEMMI score, admission National Institute of Health Stroke Scale (NIHSS) score, age, and core lesion volume in CT-perfusion. The power to discriminate between subsequent non-malignant and malignant infarction was highest for a NEMMI score >10.5 (AUC: 0.84, sensitivity: 93.3%, specificity: 70.7%, Youden J: 0.64), followed by core lesion volume (AUC: 0.80), age (AUC: 0.76), and NIHSS (AUC: 0.61).

To our knowledge, this study is the first to describe a simple imaging-based method to predict MMI at an early stage that does not require extensive post-processing, or time-consuming measurements.

The ASPECT (Alberta Stroke Program Early CT) score is a well-established imaging parameter for hypodense lesion involvement in acute MCA occlusion (23–25). Nevertheless, since the subterritorial regions assessed by the ASPECT score are each of different size but still count equally in terms of cumulative region involvement, it is not a quantitative score with respect to volume of affected tissue. In contrast, the proposed NEMMI score incorporates direct lesion diameters independent of the subterritorial location. As severity of brain swelling with mass effect is directly linked to baseline volume of edematous brain tissue, a score based on lesion dimensions rather than region involvement may be of advantage for MMI prediction (12, 23, 26).

The NEMMI score showed a high diagnostic power to predict a malignant infarction (AUC: 0.84), similar to CTP-derived core lesion volume (AUC: 0.76), or clinical parameters (NIHSS, AUC: 0.61; age, AUC: 0.76). If validated on a larger patient cohort, this would support rapid risk-stratification of early decompressive therapy in patients with MCA occlusion independent of the availability of advanced stroke imaging. Furthermore, the NEMMI score addresses a common problem in detection of early ischemic changes on admission NECT: subtleness of the early lesion in relation to the extent of the lesion. While lesions may be large in size, the hypodensity

may only be subtle and vice versa. The intensity of the edema is incorporated by grading the hypoattenuation of the early lesion on a quasi-quantitative scale (3-point visual grading of the hypodense lesion, no/subtle/clear, 1–3). Other studies have demonstrated hypodense NECT changes in more than 50% of the MCA territory as independent predictor of MMI (8, 9). This method requires volumetry of the ischemic changes and does not take into account the degree of the density changes. Nevertheless, further studies are necessary to compare different predictors of MMI in NECT with respect to predictive quality and acquisition speed.

**TABLE 2 |** Multivariable logistic regression analysis for risk analysis of MMI.

| | Odds ratio | 95%CI | *P*-value |
|---|---|---|---|
| Age | 0.93 | 0.87–1 | 0.055 |
| NIHSS at admission | 1.15 | 0.95–1.39 | 0.15 |
| NEMMI | 1.33 | 1.13–1.56 | 0.001 |
| Time from onset to imaging | 0.22 | 0.06–0.79 | 0.02 |
| Core lesion volume | 0.99 | 0.95–1.04 | 0.71 |
| Successful recanalization | 0.04 | 0–0.39 | 0.006 |

*NIHSS, National Institute of Health Stroke Scale; CI, confidence interval; NEMMI, non-enhanced malignant media infarction.*

In this study, core lesion volume was not associated with MMI in multivariable logistic regression analysis (**Table 2**), which is in accordance with recent studies observing that core lesion volume is not associated with functional outcome in low ASPECTS patients (27). Second, core lesion volume did not modify the effect of mechanical thrombectomy according to a recent meta-analysis (28).

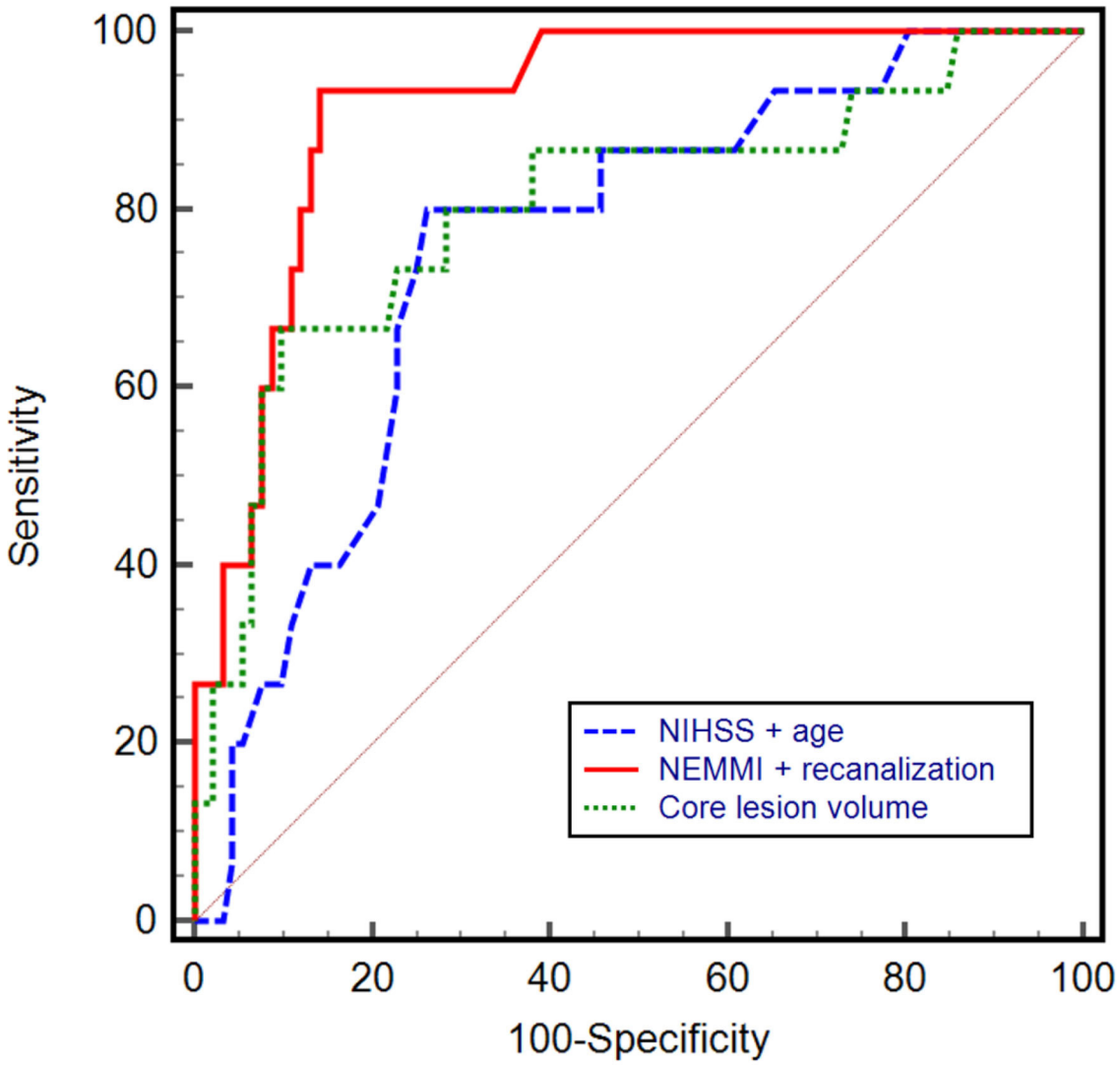


**FIGURE 5 |** Receiver operating characteristic (ROC) curves with the corresponding area under the curve (AUC) of different prediction models. A combined model including the NEMMI score and recanalization status demonstrated the highest diagnostic power (AUC: 0.92, 95%CI: 0.85–0.96), compared to the clinical model NIHSS + age (AUC 0.78; 95% CI 0.69–0.85) and core lesion volume (AUC 0.80; 95% CI 0.72–0.87). Not shown in the graph for reason of clarity: NEMMI score + age + recanalization (AUC 0.92; 95%CI 0.86–0.97); NIHSS + age + recanalization (AUC 0.89; 95%CI 0.81–0.94), NIHSS + recanalization (AUC 0.84; 95%CI 0.76–0.9).

We do not suggest that an elevated NEMMI score alone would serve as an indication for decompressive surgery. The score may rather facilitate decision making as it provides information about both lesion extent and progression in an acute clinical setting with high availability, applicability, and acquisition speed.

Further internal and external validation of the NEMMI score is necessary in a large patient cohort. Moreover, future studies should investigate how treatment factors such as successful or failed recanalization impact the predictive power of the score (29).

A major limitation of the current study and the proposed NEMMI score is the potentially compromised interrater reliability of the visually assessed hypoattenuation factor. The visual differentiation between a subtle or clearly demarcated hypoattenuation depends on various factors, such as type of scanner, image quality, slice thickness etc. An exact range of intensities (i.e., Hounsfield units) is difficult to define and would have to be adjusted for these variables. In contrast, experienced radiologists (in our study >5 years clinical practice) can judge hypoattenuations in scans acquired on a familiar scanner and with a standardized imaging protocol in a timely manner with acceptable objectiveness. Visual ratings in our study correlated significantly with NWU as semi-automatic standard measurement of ionic/vasogenic tissue edema and hence tissue hypoattenuation (12). While also interrater reliability was robust for both the measurement of the lesions diameters and the hypoattenuation factor, future studies aiming to validate the score will have to quantify this effect among various raters. Important in this context will be the simultaneous semi-automatic assessment of the NWU as independent marker of lesion hypodensity in order to either calibrate the visual grading or to serve as an objective parameter for comparison (30).

Due to strict inclusion criteria and narrow definition of malignant infarction the current study relies on a small patient sample and has therefore limited generalizability. Validation studies on a larger patient cohort will have to focus on the exact validity of the NEMMI score for prediction of MMI, ideally with definition of thresholds dependent on subsequent endovascular therapy and degree of recanalization. In the pre-thrombectomy era, prevalence of MMI was up to 10% in patients with MCA occlusion and significantly reduced during the era of endovascular thrombectomy (2, 31, 32).

## CONCLUSION

The NEMMI score is a quick and simple rating tool of early ischemic changes on non-enhanced admission CT without the necessity of multimodal imaging or time-consuming image post-processing. If validated on a larger patient cohort, it may serve as surrogate marker for developing malignant edema and hence facilitate early triage of patients for invasive monitoring or decompressive hemicraniectomy.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Hamburg Chamber of Physicians (Hamburg, Germany). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

MB and GB conceptualized and supervised the study, acquired and analyzed the data, and wrote the manuscript. SB acquired the data. JF and UH analyzed the data and critically reviewed the manuscript. LM, NH, TF, and RM critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Interaction Effect of Baseline Serum Glucose and Early Ischemic Water Uptake on the Risk of Secondary Hemorrhage After Ischemic Stroke

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**Background and Purpose:** Intracerebral hemorrhage (ICH) after mechanical thrombectomy (MT) for acute ischemic stroke (AIS) remains a major complication and its early prediction is of high relevance. Baseline serum glucose (BGL) is a known predictor of ICH, but its interaction with early ischemic changes remains uncertain. We hypothesized that BGL interacts with the effect of tissue water uptake on the occurrence of ICH.

**Methods:** Three hundred and thirty-six patients with acute ischemic stroke treated with MT were retrospectively analyzed. ICH was diagnosed within 24 h on non-enhanced CT (NECT) and classified according to the Heidelberg Bleeding Classification. Early tissue water homeostasis has been assessed using quantitative lesion net water uptake (NWU) on admission CT. Multivariate logistic regression was used to identify predictors of ICH.

**Results:** One hundred and seven patients fulfilled the inclusion criteria of which 37 (34.6%) were diagnosed with ICH. Patients with ICH had a significant higher BGL on admission (median 177 mg/dl, IQR: 127–221.75, $P < 0.001$). In patients with low BGL (<120 mg/dl), higher NWU was associated with 1.34-fold increased likelihood of ICH, while higher NWU was associated with a 2.08-fold increased likelihood of ICH in patients with a high BGL (>200 mg/dl). In multivariable logistic regression analysis, BGL (OR: 1.02, 95% CI: 1.00–1.04, $P = 0.01$) and NWU (OR: 2.32, 95% CI: 1.44–3.73, $P < 0.001$) were significantly and independently associated with ICH, showing a significant interaction ($P = 0.04$).

**Conclusion:** A higher degree of early tissue water uptake and high admission BGL were both independent predictors of ICH. Higher BGL was significantly associated with accelerated effects of NWU on the likelihood of ICH. Although a clear causal relationship remains speculative, stricter BGL control and monitoring may be tested to reduce the risk of ICH in patients undergoing thrombectomy.

**Keywords: glucose, edema, stroke, intracerebral hemorrhage, outcome**

## INTRODUCTION

Large randomized controlled trials provide efficacy of mechanical thrombectomy (MT) over medical treatment in patients with acute ischemic stroke (AIS) (1, 2). Irrespective of this success, intracerebral hemorrhage (ICH) remains a common and challenging complication with a negative impact on functional outcome. It is these very trials that have further verified a steady rate of symptomatic intracerebral hemorrhage (sICH) with 4.4% after MT when compared with intravenous thrombolysis (1). In addition, also asymptomatic ICH (aICH) has proven to have a negative impact on long-term functional outcome (3–6). Therefore, evaluating the risk factors for ICH becomes an important issue for continuously improving the efficacy of MT in patients with AIS. In patients with AIS, hyperglycemia has been a long recognized and frequent finding with up to 50% (7, 8) and repeatedly associated with increased bleeding events after thrombolytic therapy (IVT) and poor functional outcome (7–10). Furthermore, a linear relationship between increasing serum glucose and ischemic brain edema has been elucidated (11) and the latter is an independent risk factor for ICH after successful MT. The current state of literature provides no sufficient data for the mutual impact of serum glucose and early ischemic brain edema on the risk of ICH in patients with AIS (12–14). Utilizing the widely accepted Heidelberg Bleeding Classification (15), the objectives of the present study were to analyze the mutual impact of serum glucose and ischemic brain edema on the risk of ICH in patients with AIS after successful MT and, in particular, to investigate whether different glucose levels modify the effect of early edema formation on clinical outcome. We hypothesized that baseline serum glucose levels interact with the effect of early ischemic brain edema on functional outcome.

## METHODS

### Patients

Data of an anonymized cohort of 107 consecutive AIS patients with occlusion in the anterior circulation were retrospectively evaluated, in whom successful MT (TICI 2b/3) was performed (**Figure 1**). Patients were admitted between June 2015 and March 2018 in the University Medical Center Hamburg-Eppendorf ($n = 336$). Data were analyzed after ethical board approval, and informed consent was waived by the institutional review board. The data that support the findings of this study are available from the corresponding author in accordance with the institution's data security regulations upon reasonable request. The patients were screened consecutively based on the following *a priori* defined inclusion criteria: (1) acute ischemic stroke with occlusion of the middle cerebral artery (MCA) or terminal internal carotid artery (ICA), (2) initially performed multimodal CT protocol with CT angiography (CTA) and perfusion CT (CTP), (3) known time from symptom onset to imaging <6 h, (4) follow-up CT (FU-NECT) within 24 h after admission imaging, (5) NIHSS score above 3, (6) documented NIHSS after 24 h and modified Ranking Scale (mRS) after 90 days, and (7) absence of pre-existing thromboembolic or hemodynamic infarctions in admission non-enhanced CT (NECT) within 24 h of stroke symptom onset. Baseline clinical characteristics including baseline serum glucose (BGL) and demographic information were filtered from the medical records. The follow-up CT (FCT) was analyzed for secondary ICH.

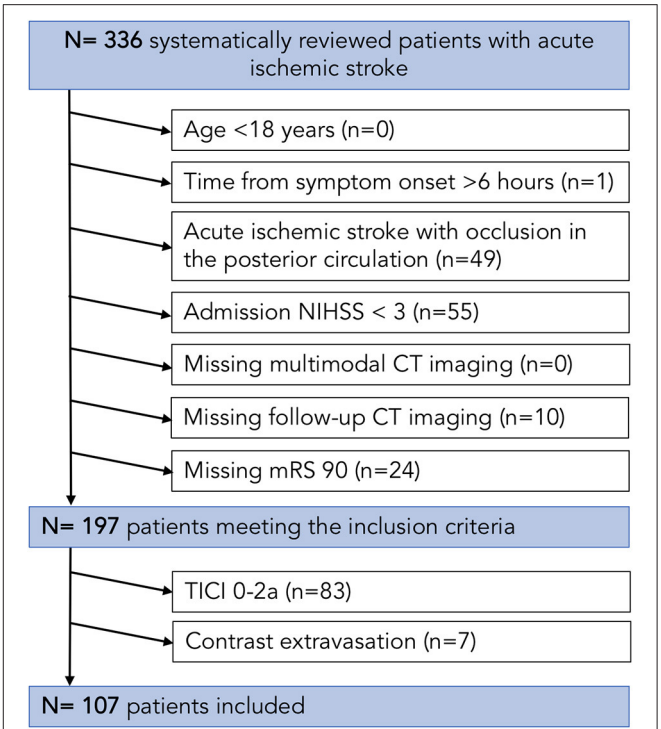



**FIGURE 1 |** Patient flowchart. CT, computed tomography; NIHSS, National Institutes of Health Stroke Scale (NIHSS); TICI, thrombolysis in cerebral infarction.

### Image Acquisitions

All CT scans were performed on 256 slice scanners (Philips iCT 256) with the following imaging parameters: NECT with 120 kV, 280–320 mA, 5.0 mm slice reconstruction; CTA: 100–120 kV, 260–300 mA, 1.0 mm slice reconstruction, 5 mm MIP reconstruction with 1 mm increment, 0.6-mm collimation, 0.8 pitch, H20f soft kernel, 80 ml highly iodinated contrast medium and 50 ml NaCl flush at 4 ml/s; scan starts 6 s after bolus tracking at the level of the ascending aorta; CTP: 80 kV, 200–250 mA, 5 mm slice reconstruction (max. 10 mm), slice sampling rate 1.50 s (min. 1.33 s), scan time 45 s (max. 60 s), biphasic injection with 30 ml (max. 40 ml) of highly iodinated contrast medium with 350 mg iodine/ml (max. 400 mg/ml) injected with at least 4 ml/s (max. 6 ml/s) followed by 30 ml sodium chloride chaser bolus. All perfusion datasets were inspected for quality and excluded in case of severe motion artifacts.

### Image Analysis

For image analysis, anonymized CT imaging scans were evaluated independently by two radiologists with 5 (JN) and 7 (GB) years of dedicated neuroradiology experience, blinded to all clinical and imaging information except stroke side.

## Collateral Score

CTA collaterals were assessed independently on admission intracranial CTA MIPs and scored according to the grading system of Souza et al. (16) into grades 0 to 4: CS: 0 = absent collaterals in >50% of an MCA M2 branch (superior or inferior division) territory; 1 = diminished collaterals in >50% of an MCA M2 branch territory; 2 = diminished collaterals in <50% of an MCA M2 branch territory; 3 = collaterals equal to the contralateral hemisphere; and 4 = increased collaterals. In addition, collateral grades were grouped into good (collateral score 3–4), partial (collateral score 2), and poor (collateral score 0–1) (14). Calculated Cohen's kappa for interrater reliability was 0.91. Collaterals were dichotomized into poor collaterals as grade 0–2 and good collaterals as 3–4 (14).

## Quantification of Ischemic Brain Edema

Anonymized admission CT imaging scans were segmented semimanually using commercially available software (Analyze 11.0, Biomedical Imaging Resource, Mayo Clinic, Rochester, MN, USA) to derive net water uptake (NWU). The edematous proportion of the hypoattenuated ischemic lesion (% water uptake) was quantified using CT densitometry as previously published (17, 18). In brief, edematous volumetric changes of ischemic lesions due to water uptake were directly quantified by measurements of relative hypoattenuation (Equation 1). Visually evident edematous hypoattenuation was identified as infarct core lesion for further analysis, and a region of interest (ROI) was placed in this infarct core lesion (*D*ischemic). A symmetric ROI was mirrored automatically within the normal tissue of the contralateral hemisphere in order to obtain the density of the normal tissue prior to the infarction (*D*normal) (19–21). CT perfusion was used in addition to aid ROI definition of the early ischemic core by simultaneously presenting cerebral blood volume (CBV) parameter maps at a window between 0 and 6 ml/100 ml (19–22). ROIs were segmented with semiautomatic edge detection and sampled between 20 and 80 HU as described by Broocks et al. (19–22). Inaccuracies were corrected in consensus reading, if necessary. Relative NWU was calculated based on $D_{\text{ischemic}}$ and *D*normal according to Equation 1.

Equation 1 (19–21):

$$\%\ water\ uptake = \left(1 - \frac{Dischemic}{Dnormal}\right) \times 100 \qquad (1)$$

## Intracranial Hemorrhage Classification

ICH diagnosis and classification was performed on FU-NECT according to the Heidelberg Bleeding Classification (15). All patients with a hyperdense phenomena without mass effect on first follow-up CT at 24 h received a minimum second follow-up CT for evaluation of contrast extravasation. Contrast extravasation was classified with a disappearance with 24 h on second FU-NECT (23).

## Statistical Analysis

Data were tested for normality and homogeneity of variance using histogram plots and Kolmogorov–Smirnov-tests. Absolute and relative frequencies are given for categorical data. Median and interquartile range (IQR) are given for univariable distribution of metric variables. Patients with ICH vs. without ICH were compared by Mann–Whitney *U*-test for metric outcome variables and by chi-square test for categorical outcome variables (**Table 1**). Kappa statistic and calculated Cohen's *k* were used for interrater reliability measurement. ROC analysis was assessed to analyze the diagnostic performance for prediction of ICH after successful MT using increasing discrimination thresholds of independent predictors and cutoffs determined according to the Youden index (24, 25). The association between clinical and radiological parameters and ICH in patients after successful MT was assessed by univariate logistic regression analysis. For multivariate logistic regression analysis, a model with forward selection was used to identify significant variables for developing ICH (inclusion criterion: *P*-value of the score test ≤0.05, exclusion criterion: *P*-value of the likelihood ratio test >0.1) (**Table 2**). Given for selected variables are odds ratio (OR) with 95% CI and *P*-value of likelihood ratio test. For non-selected variables, *P*-value of score test is displayed. The impact of BGL on the association of NWU and occcurence of ICH was tested using logistic regression analysis. The OR for NWU increase was assessed for patients with five different levels of blood glucose based on the relative distribution of BGL (**Table 3**). Finally, to further analyze the relationship of early edema formation and BGL, we trichotomized patients into three groups based on the distribution of NWU within the patient cohort. The interaction term for trichotomized NWU and BGL was calculated and plotted (**Figure 2**). A statistically significant difference was accepted at a *P*-value of <0.05. No adjustment for mutlitple testing was performed as the analyses being explorative in nature. Analyses were performed using MedCalc (version 11.5.1.0; Mariakerke, Belgium) and Stata/SE 13.0 (StataCorp, College Station, TX, USA).

# RESULTS

## Patients

Out of 336 patients, 107 consecutive patients were included according to the inclusion criteria [median age 76 years (IQR: 65.0–81.0) and 51.4% females] with 63 patients (58.9%) having received intravenous thrombolysis before MT. An example is illustrated in **Figure 3**. Thirty-seven patients (34.6%) had an ICH within 24 h after MT according to the Heidelberg Bleeding Classification with sICH identified in 19 patients (17.8%). Admission NIHSS was significantly higher in patients with ICH ($P = 0.005$). Also, both significantly higher NIHSS after 24 h and at discharge were observed in patients with ICH ($P < 0.001$). Further patient characteristics are summarized in **Table 1**. A history of diabetes was present in 20 (18.7%) patients with no statistical differences between patients with and without ICH ($P = 0.63$). The median blood glucose level at admission was 134 mg/dl (IQR: 110.0–178.5) with significant higher levels in patients with ICH 177 mg/dl (IQR: 127–221.75) vs. 126 mg/dl (IQR: 106–147) in patients without ICH ($P < 0.001$). CT-based derived parameters of quantitative NWU and collateral score were significantly different for both groups with a higher NWU in patients with ICH (13%; IQR: 11–16%) and lower collateral

**TABLE 1 |** Comparison of demographic, clinical, and radiological characteristics between patients with intracerebral hemorrhage and those with no intracerebral hemorrhage after successful mechanical recanalization.

| Baseline characteristics | All ($n = 107$) | Without ICH ($n = 70$) | With ICH ($n = 37$) | *P*-value |
|---|---|---|---|---|
| Age (years), median (IQR) | 76 (65.0; 81.0) | 75 (64.8; 80.0) | 79 (69; 84) | 0.074 |
| Female, *n* (%) | 55 (51.4) | 34 (48.6) | 21 (56.8) | 0.420 |
| Hypertension, *n* (%) | 60 (56.1) | 36 (51.4) | 24 (64.9) | 0.183 |
| Diabetes mellitus, *n* (%) | 20 (18.7) | 14 (20.0) | 6 (16.2) | 0.633 |
| Atrial fibrillation, *n* (%) | 39 (36.4) | 19 (27.1) | 20 (54.1) | 0.006 |
| Smoking, *n* (%) | 15 (16.9) | 10 (18.2) | 5 (14.7) | 0.670 |
| Dyslipidemia, *n* (%) | 23 (21.5) | 16 (22.9) | 7 (18.9) | 0.637 |
| Blood glucose (mg/dl), median (IQR) | 135 (110.25; 178.5) | 126 (106.5; 147) | 177 (127; 221.75) | <0.001 |
| **CT parameters, median (IQR)** | | | | |
| • ASPECTS | 8 (6; 9) | 8 (6.0; 9.0) | 7 (5.5; 8.0) | 0.02 |
| • Collateral score | 2 (1.0; 3.0) | 2 (2.0; 3.0) | 1 (1.0;2.0) | <0.001 |
| • Net water uptake (NWU) | 0.04 (0.00; 0.1) | 0.05 (0.03; 0.09) | 0.13 (0.1; 0.16) | <0.001 |
| **Stroke cause, *n* (%)** | | | | 0.054 |
| • Cardioembolic | 56 (52.3) | 33 (47.1) | 23 (62.2) | |
| • Large-artery atherosclerosis | 42 (39.3) | 28 (40.0) | 14 (37.8) | |
| • Others | 9 (8.4) | 9 (12.9) | 0 (0) | |
| **Procedure process and results** | | | | |
| • General anesthesia, *n* (%) | 75.0 (70.1) | 52 (74.3) | 14 (37.8) | 0.193 |
| • Intravenous thrombolysis, *n* (%) | 63 (58.9) | 26 (37.1) | 19 (51.4) | 0.250 |
| • OTI (h), median (IQR) | 2:35 (1:06; 3:44) | 2:24 (0:59; 3:42) | 2:40 (2:07; 3:51) | 0.438 |
| • ITR (h), median (IQR) | 1:47 (1:23; 2:03) | 1:40 (1:19; 1:58) | 1:53 (1:33; 2:10) | 0.243 |
| • Passes of retriever | 2 (1; 2) | 2 (1; 2) | 2 (1; 3) | 0.071 |
| • mTICI (2b, 3 grouped), *n* (%) | 107 (100) | 70 (100) | 37 (100) | 0.486 |
| **Clinical parameters** | | | | |
| • NIHSS on admission | 13 (12; 19) | 15 (12.0; 18.0) | 19 (16.0; 20.0) | 0.005 |
| • NIHSS after 24 h | 3 (5; 20) | 10 (4.0; 16.0) | 19 (13.0; 34.5) | <0.001 |
| • NIHSS at discharge | 1.5 (3; 14) | 5 (1.0; 9.8) | 14 (7.5; 18.5) | <0.001 |
| **90-day mRS, median (IQR)** | 4 (3.2; 4.0) | 3 (2.5; 3.6) | 5 (4.3; 5.3) | <0.001 |
| • 0–1, *n* (%) | 28 (28.0) | 25 (37.3) | 3 (9.1) | 0.003 |
| • 2–3, *n* (%) | 15 (15) | 11 (16.4) | 4 (12.1) | 0.572 |
| • 4–6, *n* (%) | 55 (51.4) | 29 (44.6) | 26 (78.8) | 0.001 |

*ICH, intracerebral hemorrhage; IQR, interquartile range; TICI, thrombolysis in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale; TICI, thrombolysis in cerebral infarction; INR, international normalized ratio.*

score (1; IQR: 1–2) vs. lower NWU (5%; IQR: 3–9%) and higher collateral score (2; IQR: 2–3) in patients without ICH. Baseline Alberta Stroke Program Early CT (ASPECTS) was statistically different between both groups, with ASPECTS 7 in patients with ICH (IQR: 5.5–8) and ASPECTS 8 in patients without ICH (IQR: 6–9, $P = 0.02$). Unfavorable clinical outcome at 90 days (mRS score 4–6) was higher in patients with ICH (78.8 vs. 44.6%, $P = 0.001$). Excellent clinical outcome (mRS score 0–1) at 90 days was higher in patients without ICH (37.3 vs. 9.1% with ICH, $P = 0.003$). **Figure 4** illustrates the relationship of BGL and NWU on the occurrence of ICH.

**TABLE 2 |** Multivariable analysis of predictors of secondary hemorrhage after successful mechanical recanalization.

| Serum glucose (mg/dl) | OR for ICH | 95% CI | *P*-value |
|---|---|---|---|
| Net water uptake (NWU; per %) | 2.31 | 1.33–3.73 | <0.001 |
| Collateral score (ref: poor) | 0.05 | 0.008–0.27 | 0.0007 |
| Blood glucose (mg/dl) | 1.02 | 1.00–1.04 | 0.01 |

*Non-significant independent variables are not displayed. Given for selected variables are odds ratios (OR) with 95% confidence interval (CI) and P-value of likelihood ratio test. ICH, intracerebral hemorrhage.*

## Prediction of ICH

Univariate ROC analysis was performed to identify the diagnostic accuracy of independent variables of univariate logistic regression. NWU with an optimal cutoff above 8% predicted ICH with the highest discriminative power [area under the curve (AUC): 0.90, 95% CI: 0.82–0.95; specificity 74.3%,

**TABLE 3 |** The association of NWU and occurrence of secondary hemorrhage after successful mechanical recanalization, mediated by different baseline serum glucose levels.

| Serum glucose (mg/dl) | OR for NWU (per %) | 95% CI | *P*-value |
|---|---|---|---|
| <120 | 1.34 | 1.00–1.79 | 0.05 |
| <134 (median) | 1.39 | 1.09–1.78 | 0.008 |
| >134 | 1.63 | 1.24–2.13 | 0.0005 |
| >150 | 1.87 | 1.22–2.87 | 0.004 |
| >170 | 2.08 | 1.10–3.92 | 0.02 |

*Odds ratios (OR) for net water uptake (NWU) given for selected levels of serum blood glucose with 95% confidence interval (CI) and P-value of likelihood ratio test.*

sensitivity 97.3%, $P < 0.0001$], followed by collateral score with an optimal cutoff below 1 (AUC: 0.81, 95% CI: 0.72–0.89; specificity 84.4%, sensitivity 67.7%, $P < 0.0001$) and admission serum glucose with an optimal cutoff above 147 mmol/L (AUC: 0.82, 95% CI: 0.73–0.89; specificity 74.3%, sensitivity 75.7%, $P < 0.011$; **Figure 5**).

Logistic regression analysis was performed to assess the association between various clinical and radiological parameters and the incidence of ICH after successful MT. At univariate logistic regression analysis, ICH was predicted by higher admission serum glucose (OR 1.01 per median, 95% CI: 1.00–1.02, $P = 0.048$), lower collateral score (OR 0.37 per median, 95% CI: 0.20–0.67, $P < 0.001$), high admission NIHSS (OR: 1.08, 95% CI: 1.01–1.15, $P = 0.027$), low ASPECTS (OR: 0.78, 95% CI: 0.61–0.99, $P = 0.041$), and higher early NWU (OR: 1.56, 95% CI: 1.31–1.86, $P < 0.0001$). In multivariable logistic regression analysis, a higher degree of NWU (adjusted OR 2.31 per %, 95% CI: 1.33–3.73, $P = 0.0006$), a lower collateral score (adjusted OR 0.05 per median, 95% CI: 0.008–0.27, $P = 0.0007$), a lower ASPECTS (OR: 2.71, 95% CI: 1.31–5.61, $P = 0.007$), and a higher BGL (adjusted OR 1.02 per median, 95% CI: 1.00–1.04, $P = 0.01$) were identified as independent predictors of ICH after successful MT (**Table 2**). Higher admission NIHSS was not significantly associated with ICH (OR: 1.06, 95% CI: 0.94–1.2, $P = 0.35$).

## Interaction of NWU and BGL

We tested how the likelihood for ICH by increasing NWU is associated with concordant increasing levels of BGL. For patients with lower BGL (<134 mg/dl, median), higher NWU was associated with a 1.39-fold likelihood for ICH, while for patients with higher BGL (>134 mg/dl), NWU increase was associated with 1.63-fold likelihood for ICH. For patients with very high BGL (>170 mg/dl), a NWU increase was associated with a 2.08-fold likelihood for ICH (**Table 3**). Finally, NWU was trichotomized into low (<7%), intermediate (7–12%), and high NWU (>12%). A higher trichotomized NWU was significantly associated with increased likelihood of ICH (OR: 9.41, 95% CI: 3.81–23.27, $P < 0.001$). The interaction term between NWU and BGL was significant (OR: 1.03, 95% CI: 1.01–1.06, $P = 0.04$; **Figure 2**).

## Subanalysis for Patients With Intermediate and High NWU but Low BGL

Finally, patients with intermediate and high NWU (>7%) but low BGL (<134 mg/dl, median) were investigated. Comparing these patients to patients with higher BGL (>134 mg/dl), there were no significant differences in age, ASPECTS, NIHSS, or time from onset to imaging. However, patients with intermediate and high NWU but low BGL showed a significantly lower collateral score (1.4 vs. 2.2, $P = 0.02$).

# DISCUSSION

Higher admission BGL as an independent predictor for developing an ICH after successful ET in AIS paired with the association between ischemic edema is the main finding of our study. Furthermore, the effect of NWU on the occurrence of ICH was increased in patients with higher BGL suggesting a specific interrelation between early edema formation, as a sign of blood–brain barrier injury, and BGL as a potential "accelerator" of blood–brain barrier injury. This finding was accompanied by elevated early ischemic edema and poor collateral score as a second independent predictor for ICH. BGL and NWU showed a significant interaction indicating that the slopes for likelihood of ICH with increasing BGL differ significantly according to the degree of NWU, as illustrated in **Figure 2**. In patients with very low early NWU, BGL increase did not alter the risk of ICH, while a BGL increase in patients with higher NWU resulted in a significant increase in likelihood for ICH. The specific interaction between early edema formation and serum glucose levels and its impact on the occurrence of ICH has not yet been described and might be a hint of a specific pathophysiological association. It has been observed that elevated levels of BGL are associated with aggravated edema formation (13), as a sign of blood–barrier injury, and that elevated levels of early edema formation increased the risk of secondary hemorrhage (12). Hence, the coexistence of high BGL and high NWU might be a constellation of very high risk for ICH and should be a hint for clinicians to indicate stricter monitoring and consider adjustment of glucose levels. Moreover, the findings could enrich for patients to study experimental treatments with antiedematous drugs, such as glyburide. Glyburide, an antidiabetic drug, is an inhibitor of the sulfonylurea receptor 1 and transient receptor potential melastatin 4 (SUR1-TRPM4) (26). The application of glyburide is safe and feasible and has been described for preventing edematous brain edema (27). In previous pre-clinical studies using rodent models with malignant edema, inhibition of SUR1 resulted in lower ischemic lesion volume, reduced mortality, and better functional outcome (28). Supporting these pre-clinical data, retrospective analyses on patients with diabetes and AIS observed that patients with medication of sulfonylurea drugs had an improved clinical outcome and lower rates of hemorrhagic transformation (HT) (29).

The nature of the association between acute elevated levels of admission glucose and increased risk of ICH has already been investigated in animal models of AIS as well as in both

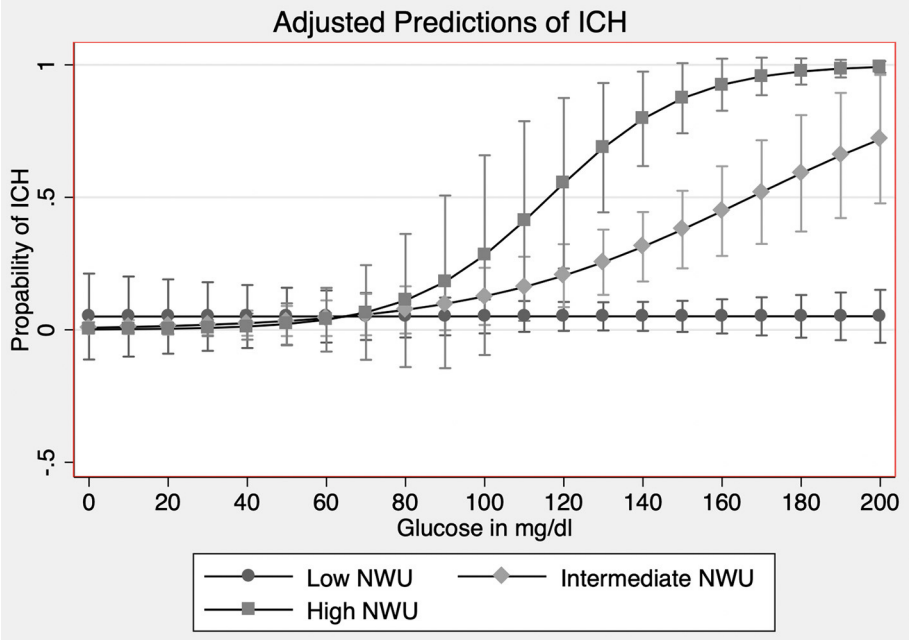



**FIGURE 2 |** Interaction analysis of BGL and NWU on the occurrence of ICH. Occurrence of secondary intracerebral hemorrhage (ICH, *y*-axis) according to trichotomized NWU (net water uptake; low NWU: <7%; intermediate NWU: 7–12%; high NWU: >12%) and BGL (baseline glucose level; glucose in mg/dl, *x*-axis). The interaction term between NWU and BGL was significant.

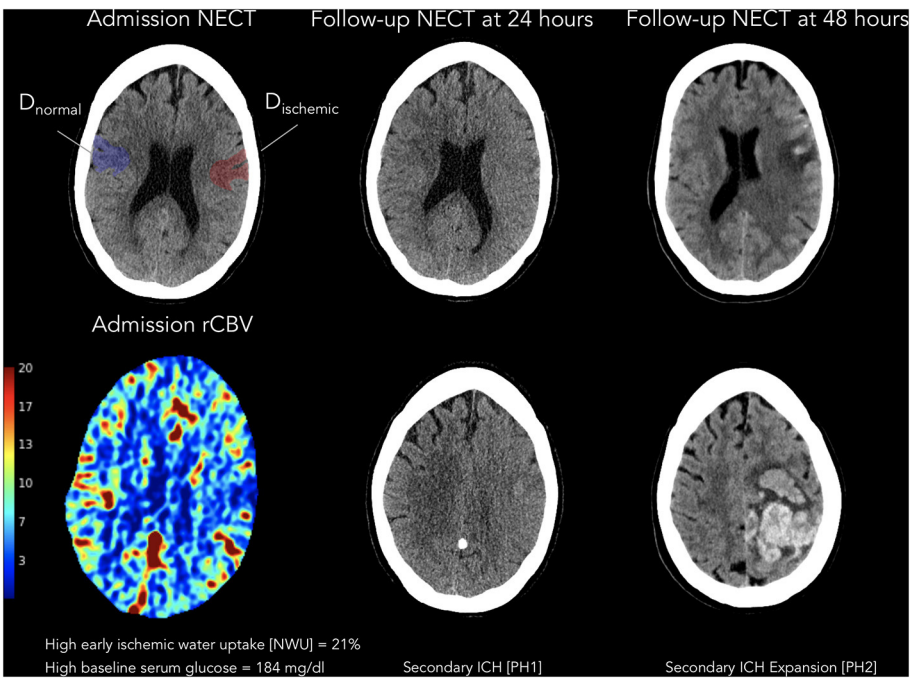



**FIGURE 3 |** Illustrative example of a patient with baseline glucose and water uptake and secondary ICH after successful thrombectomy. Illustration of a patient with high early baseline blood glucose and high ischemic water uptake, with subsequent secondary intracerebral hemorrhage after thrombectomy. On the left, patient admission images are displayed with admission non-enhanced CT and ROIs for ischemic hypoattenuation ($D_{ischemic}$) and on the contralateral side ($D_{normal}$) as well as relative CBV (rCBV). The rCBV map (ml per 100 ml) is inferred from a quantitative assessment of the partial volume averaging in each pixel. In the middle, follow-up non-enhanced CT images at 24 h are displayed with secondary intracerebral hemorrhage (parenchymal hematoma; grade 1). On the right, follow-up non-enhanced CT images at 48 h are displayed with secondary intracerebral hemorrhage (parenchymal hematoma; grade 2). rCBV, relative cerebral blood volume; NECT, non-enhanced CT; PH1, parenchymal hematoma grade 1; PH2, parenchymal hematoma grade 2.

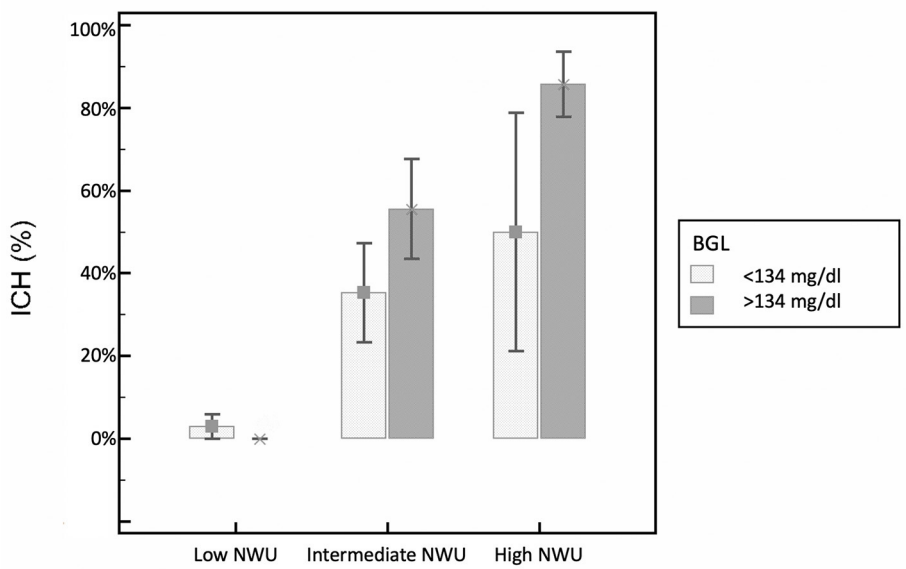
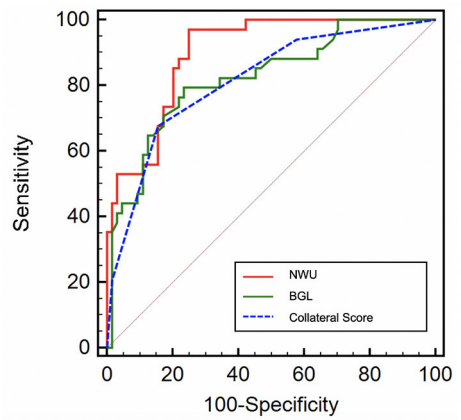



**FIGURE 4 |** Relationship of BGL and NWU on the occurrence of ICH. Occurrence of secondary intracerebral hemorrhage (ICH) according to baseline NWU (net water uptake) and BGL (baseline glucose level), separately for patients with low and high BGL (based on the median BGL) and trichotomized NWU based on relative distribution of NWU within the patient cohort (low NWU: <7%; intermediate NWU: 7–12%; high NWU: >12%).




| Variable | AUC | Cut-off | 95%CI | Sensitivity | Specificity | *P*-Value |
|---|---|---|---|---|---|---|
| NWU (%) | 0.90 | > 8% | 0.82-0.095 | 97.3 % | 74.3 % | <0.0001 |
| Collateral Score | 0.81 | < 1 | 0.72-0.89 | 67.7 % | 84.4 % | <0.0001 |
| BGL (mg/dl) | 0.82 | > 147 mg/dl | 0.73-0.89 | 75.7 % | 74.3 % | <0.001 |

**FIGURE 5 |** Receiver operating curve (ROC) analysis for the prediction of secondary hemorrhage after successful mechanical recanalization. ASPECTS, Alberta Stroke Program Early CT Score; AUC, area under the curve; 95% CI, 95% confidence interval; NWU, net water uptake; BGL, baseline glucose level.

retrospective and prospective clinical imaging studies (7, 30–33). Previous studies evaluating the risk and rates of ICH have been hampered by the lack of consensus definitions for bleeding events (31). The recently introduced Heidelberg Bleeding Classification provides a standardized and reproducible tool and basis for evaluating further treatment strategies (34). Nevertheless, our study is methodically limited to the important fact that a systematic approach in classifying symptomatic ICH is missing which should be addressed in future clinical studies with larger patient cohorts. The quantitative stratification of ischemic brain edema *via* NWU demonstrates the direct relation of hypoattenuation in CT to the percentage of volume of water uptake and has been validated with excellent sensitivity and reproducibility since (19, 20, 35). Recent findings of our study group give two major explanatory reasons for poor clinical outcome after MT and the risk of an ICH. Firstly, poor clinical outcome has been associated with increased levels of ischemic edema and further associated with poor collateral score and elevated BGL (12, 13, 36). Secondly, collaterals and the degree of NWU both mediate tissue vulnerability and the risk for an ICH (12). In line with this, the recently published study of Hao et al. also reported poor collateral circulation as an independent predictor for ICH (37). Yet, the relationship of NWU and hyperglycemia with respect to the occurrence of ICH after successful MT remains unknown. The pathophysiology adds support to our hypothesis as both elevated BGL and ischemic edema share a common pathway of impaired blood–brain barrier (BBB) with the risk of increased tissue vulnerability: ICH after MT occurs due to a reperfusion syndrome from rupture of necrotic vessel walls and increased BBB permeability due to prolonged ischemia (38, 39). By mediating both oxidative stress and inflammation response in vessel walls, hyperglycemia is also associated with increased reperfusion injury (40–42). The aggravated breakdown of the

BBB results in further edema formation and increased infarct volume (8, 43). Thorén et al. have investigated the impact of hyperglycemia on admission as an independent risk factor for cerebral edema in patients with AIS treated with IVT and obtained the extent of ischemic edema with a visual rating system (11). This study is in concordance with our previous findings that proved that the degree of early edema formation using a quantitative imaging biomarker is a risk factor for secondary ICH, possibly potentiated by increased levels of BGL (12, 38, 39). Taken all together, these independent variables may provide a closed loop that provides a target for therapeutic intervention to disrupt the cycle. Further clinical studies analyzing the mediated effect of NWU on the risk of ICH by increased levels of BGL are therefore needed. Also, potential beneficial treatment effects from the control of hyperglycemia in patients with AIS have been described numerously (44), yet established treatment methods are still under investigation. Although results from experimental studies support a causal relationship between hyperglycemia and poor functional outcome after stroke, multicenter trial data presented in the SHINE, GIST-UK, or THIS trial do not yet support intervention with insulin (45–47). In the future, clinical trials might consider combining reperfusion with further adjuvant treatment in patients with AIS and elevated levels of admission glucose. Yet, standardized methods to monitor possible effects on ischemic tissue edema are still missing. In this respect, quantitative NWU might provide a feasible imaging biomarker to monitor the effects of these drugs in prospective clinical trials, subject to the condition of a confirmed mediated effect of NWU by BGL (26, 27, 48).

Several limitations of our study deserve attention. First, for the assessment of NWU measurements, ROIs were drawn by a quantitative edge detection tool and boundaries adjusted manually if necessary, for example, in cases of anatomical asymmetry which may hamper NWU quantification. However, semiautomatic methods of Hounsfield unit value thresholding have been used in our previous studies with excellent reproducibly and partially mitigate a method bias (17, 21). Interrater reliability may further help to augment the accuracy of NWU measurements in the future. Additionally, the lack of information on the longitudinal course of glucose levels upon FU-NECT and the undocumented use of blood glucose-lowering drugs limit the generalizability of our results. Furthermore, the purpose of this study was to predict secondary ICH without further differentiating into symptomatic or asymptomatic ICH. As it has been observed in both retrospective and prospective studies that asymptomatic ICH is also associated with worse functional outcome, we nevertheless consider our observation to be of importance (4–6). In light of these findings, it is relevant to investigate the risk factors for any ICH, to finally improve the prevention of ICH in patients undergoing MT. Finally, according to the retrospective nature of the study, no causality assumptions can be inferred from the obtained data.

## CONCLUSIONS

Our study confirmed that higher BGL increased the likelihood for ICH, but depends on the degree of early ischemic edema. Although a causal relationship between NWU and higher BGL and ICH remains speculative and more data are needed, specific interactions between BGL and NWU may be tested as a further therapeutic target.

## DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: According to the institution's strict data security regulations the entire datasets are not publicly available. Requests to access these datasets should be directed to jawed.nawabi@charite.de.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ärztekammer Hamburg WF-035/18. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

All authors listed have made substantial, direct and intellectual contribution to the work and approved it for publication.

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BRIEF RESEARCH REPORT
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# Value of Dual-Energy Dual-Layer CT After Mechanical Recanalization for the Quantification of Ischemic Brain Edema

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**Background and Purpose:** Ischemic brain edema can be measured in computed tomography (CT) using quantitative net water uptake (NWU), a recently established imaging biomarker. NWU determined in follow-up CT after mechanical thrombectomy (MT) has shown to be a strong predictor of functional outcome. However, disruption of the blood–brain barrier after MT may also lead to contrast staining, increasing the density on CT scans, and hence, directly impairing measurements of NWU. The purpose of this study was to determine whether dual-energy dual-layer CT (DDCT) after MT can improve the quantification of NWU by measuring NWU in conventional polychromatic CT images (CP-I) and virtual non-contrast images (VNC-I). We hypothesized that VNC-based NWU (vNWU) differs from NWU in conventional CT (cNWU).

**Methods:** Ten patients with middle cerebral artery occlusion who received a DDCT follow-up scan after MT were included. NWU was quantified in conventional and VNC images as previously published and was compared using paired sample *t*-tests.

**Results:** The mean cNWU was 3.3% (95%CI: 0–0.41%), and vNWU was 11% (95%CI: 1.3–23.4), which was not statistically different ($p = 0.09$). Two patients showed significant differences between cNWU and vNWU ($\Delta = 24\%$ and $\Delta = 36\%$), while the agreement of cNWU/vNWU in 8/10 patients was high (difference 2.3%, $p = 0.23$).

**Conclusion:** NWU may be quantified precisely on conventional CT images, as the underestimation of ischemic edema due to contrast staining was low. However, a proportion of patients after MT might show significant contrast leakage resulting in edema underestimation. Further research is needed to validate these findings and investigate clinical implications.

**Keywords: net water uptake, mechanical recanalization, dual-energy computed tomography, virtual non-contrast image, brain edema, ischemia, acute stroke**

## INTRODUCTION

Randomized control trials demonstrated that mechanical thrombectomy (MT) of anterior large vessel occlusion (LVO) in acute stroke patients improves the clinical outcome compared to standard therapy (1). Yet, the clinical outcome, even after successful recanalization varies widely (2), and is subject of ongoing investigations. Different parameters influence the outcome, for example, the time from clinical onset to reperfusion, patient age, the National Institutes of Health Stroke Scale (NIHSS) at admission, the Alberta stroke program early computed tomography (ASPECT) score at admission, and the baseline functional status (3).

Recently, it has been observed that the degree of edema formation in early follow-up imaging captured by net water uptake (NWU), a quantitative imaging biomarker, is an indicator of the response to MT (4). NWU is an accurate predictor of functional outcome and outperforms clinical variables, for example, age, NIHSS, and/or ASPECTS (4). These results are in accordance with other studies describing a strong correlation between NWU quantified in CT and the final infarct volume (5, 6).

Cerebral edema is the pathophysiological response of ischemic brain tissue undergoing infarction, which is evident in CT by means of progressive tissue hypoattenuation (7). Reperfusion after LVO has been associated with increased edema formation caused by microvascular damage probably resulting in an extension of the initial infarct area (8), but recently, it has been observed that MT might reduce cerebral edema (9, 10) and is associated with a lower risk for progressive edema compared to intravenous thrombolysis (11).

Disruption of the blood–brain barrier after MT may not only lead to edema but also to hemorrhage and/or contrast staining (12), increasing the density on CT scans, and hence, directly impairing measurements of brain edema on conventional polychromatic CT images (CP-I). Lesion hyperattenuations are common findings after LVO and are described in up to 84% of patients directly after MT, and ∼20% after 24 h, which could result in an underestimation of brain edema on conventional polychromatic images (CP-I) (13). Follow-up CT is routinely performed after MT, in particular to rule out hemorrhage (14),

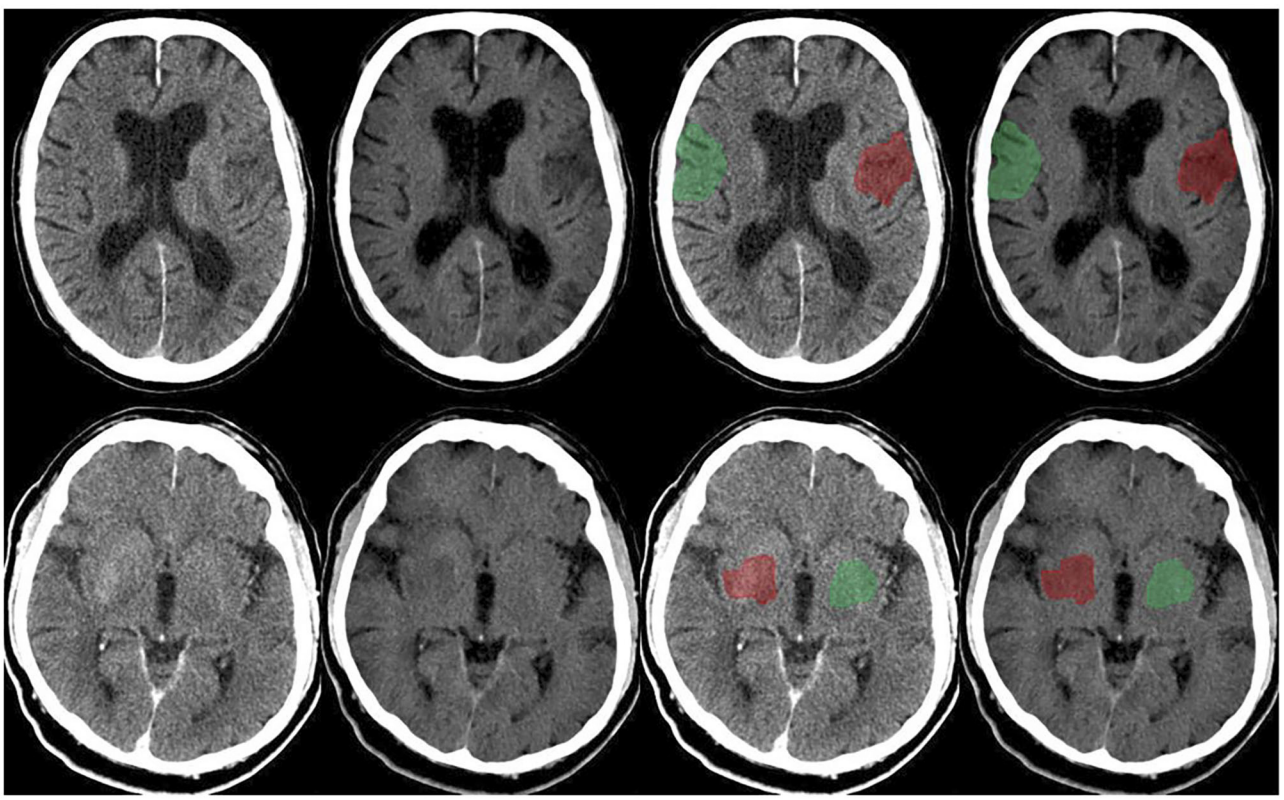

**FIGURE 1 |** Upper row: Follow-up dual-layer dual-energy CT within 12 h in a 70-year-old man with left MCA occlusion (initial NHISS 7; ASPECTS 8) after thrombectomy (TICI 3), time onset to reperfusion 184 min. Conventional polychromatic image (first and third from the left), VNC image (second and fourth from the left). Example of ischemic ROI placement (red) and contralateral normal ROI placement (green). Lower row: Follow-up dual-layer dual-energy CT within 12 h in an 89-year-old man with right MCA occlusion (initial NHISS 17; ASPECTS 8) after thrombectomy (TICI 3), time onset to reperfusion 154 min. Conventional polychromatic image (first and third from the left), VNC image (second and fourth from the left). Example of ischemic ROI placement (red) and contralateral normal ROI placement (green).

but differentiation between tissues densities of similar Hounsfield units, for example, blood and contrast medium remains difficult in this modality.

Recently, dual-energy imaging methods have become increasingly popular in research and clinical practice because of their capability to discriminate between tissues of similar X-ray attenuation but different atomic numbers (15–19). Dual-energy CT technology is based upon the light-matter interaction and different absorption characteristics of specific substances. Iodine for instance increases X-ray absorption at 32.2 keV (16, 20). Different technical methods are available to capture these characteristic absorption profiles of substances and generate dual-energy CT datasets, which can be used to calculate virtual non-contrast images (VNC-I).

Considering the clinical relevance of cerebral edema as an indicator for malignant infarction as well as for outcome prediction, we aim to investigate the potential underestimation of edema on conventional CT images due to contrast staining by using DDCT scans for VNC-based NWU quantification. We hypothesized that NWU quantification in follow-up imaging after MT differs significantly between conventional polychromatic and VNC images.

# MATERIALS AND METHODS

## Study Population

The data that support the results of this study are available from the corresponding author, upon reasonable request. The local ethics committee approved the study (Ethics Committee of the Medical Faculty of the Christian-Albrechts-University, Kiel; Number D 567/18) and waived the requirement to obtain informed consent. We retrospectively analyzed the data of 10 consecutive patients referred to our hospital between September 2019 and January 2020 who received DDCT scans of the cranium after MT of a LVO of the anterior circulation within the standard clinical protocol. MT was performed according to the ESO/ESMINT-Guidelines (21). Data was anonymized and analyzed, retrospectively.

## Image Acquisition and Reconstruction

Image acquisition was performed on a dual-energy dual-layer CT (IQon spectral CT, Philips Healthcare, USA) with 120 kVp and 230 mAs. IntelliSpace (Version 11.1, Philips Healthcare, USA) was used as post-processing software. The VNC-I and the CP-I were generated from spectral based datasets and reformatted with 5-mm slice thickness. The CP-I were reconstructed using iterative model-based reconstructions (level 1, filter UB), whereas the VNC-I were generated using a spectral reconstruction mode (level 2).

## Image Analysis

The data were analyzed using IntelliSpace (Version 11.1, Philips Healthcare, USA). The rater was blinded for all patient-related data and clinical information. A standardized procedure to quantify the proportion of ischemic edema due to NWU was used as previously published (5, 22). In summary, a region of interest (ROI) was placed for density measurements according to the extent of ischemic hypoattenuation identified on conventional images with hindsight knowledge of VNC-I, and the core lesion in CT perfusion imaging was mirrored to the unaffected contralateral brain hemisphere. ROI histograms were sampled between 20 and 80 Hounsfield units to exclude voxels belonging to calcifications or cerebrospinal fluid. Both measurements were then used to calculate the proportion of edema within the lesion, obtaining NWU of CP-I (cNWU) (23, 24). This procedure was subsequently repeated on VNC-I to calculate VNC-based NWU (vNWU).

## Statistical Analysis

Data is reported using standard descriptive statistics. All statistics were calculated using MedCalc (version 11.5.1.0, Mariakerke, Belgium). *P*-values $< 0.05$ were considered statistically significant. cNWU and vNWU were compared using paired sample *t*-tests with means and 95% confidence intervals. The difference of both measurements was compared for every patient ($\Delta$NWU = vNWU – cNWU). Bland-Altman plots were used to illustrate measurements of vNWU and cNWU for every patient (**Figure 2**).

# RESULTS

In this pilot study, 10 consecutive patients (five female and five male) were included with mean age of 81 years (range: 53–99). Within this group, patients had been examined 12h ($\pm$ 6h) after MT (median 9.5h). The pattern of vessel occlusion was nine M1-occlusions and one proximal M2-occlusion. Post-interventional TICI score was 2b-3 in nine cases and 2a in 1 case. The median ASPECTS was 8 (range: 4–10), and the mean core lesion volume defined by regional cerebral blood flow <30% was 11.5 ml (range: 0–57 ml). The median NIHSS was 14 (interquartile range: 6–18).

**Figure 1** demonstrates the CP-I and VNC-I, which were used for further image analysis. Overall, the mean NWU was 3.3% (95%CI: 0–0.41%) in cNWU and 11% (95%CI: 1.3–23.4%) in vNWU. The mean difference between cNWU and vNWU was 7.7%, which was not statistically different ($p = 0.09$).

Eight out of 10 patients showed a high agreement of NWU with a mean difference of only 2.3% between cNWU and vNWU ($p = 0.23$). Two out of 10 patients were significant outliers with high differences in NWU between cNWU and vNWU of 24 and 36%, respectively. For other aspects, these two patients were in range of the cohort. Age was 70 (86) years, ASPECTS was 8 (8), final TICI was 3 (3), core size lesion 0 (28) ml, and time from MT to follow-up CT scan was 7 h (10 h). The Bland-Altman Plot (**Figure 2**) shows the exact differences in NWU for each patient in percent.

# DISCUSSION

This is the first study to investigate VNC-I for the use of NWU quantification, targeting a potential underestimation of cerebral edema in conventional CT images due to contrast staining in stroke lesions. This was done by comparing NWU in CP-I and VNC-I from DDCT scans, using a previously published method (6). The benefit of VNC-I to visually improve the detection of

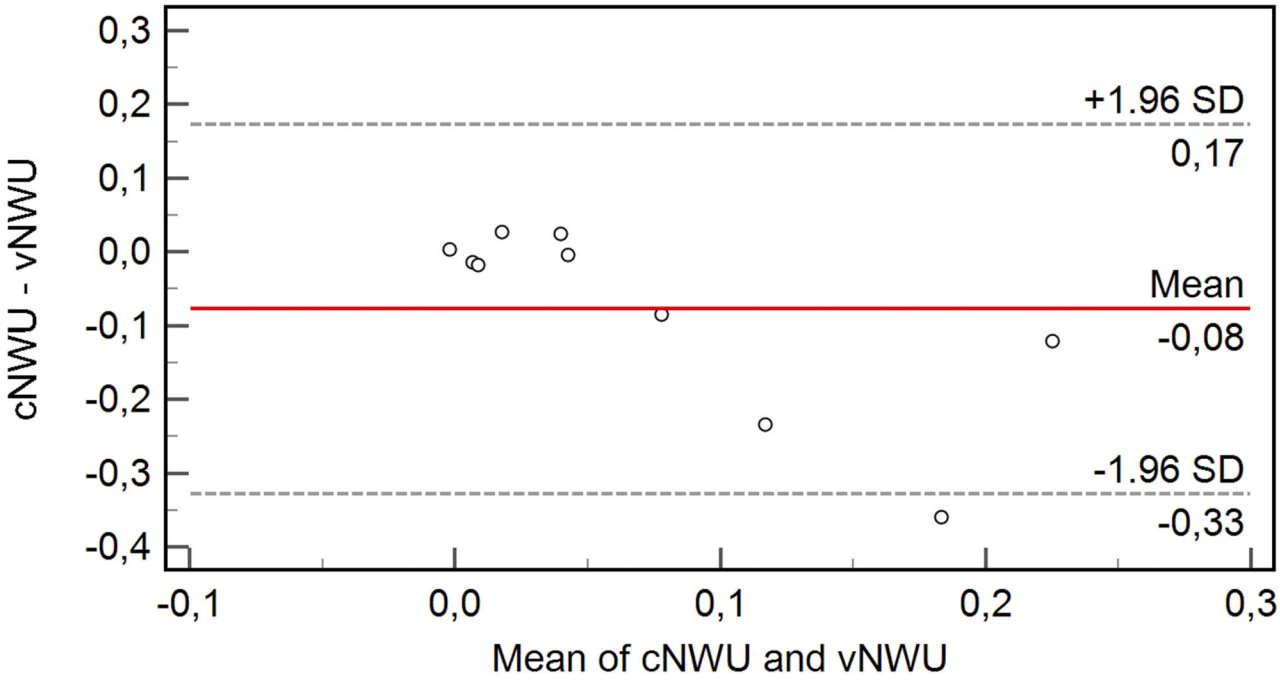


**FIGURE 2 |** Bland-Altman Plot showing the variable difference of cNWU and vNWU in percent. The mean difference between both methods was −0.08 with only one patient outside ±1.96 standard deviations.

cerebral edema in acute stroke lesions was shown (25, 26), but measuring the impact of VNC-I on NWU quantification has not been investigated before.

The main finding of this pilot study was that cNWU and vNWU did not show a significant difference in quantified NWU ($p = 0.09$). By trend, vNWU had a slightly higher NWU compared to cNWU (11 vs. 3.3.%), which was mainly caused by two outliers in our study group showing significant differences in NWU of 24 and 36%, respectively (**Figure 2**). The agreement of the other eight patients was high. This implies the possibility of a small subgroup of patients, which might show a stronger than average hyperattenuation in CP-I and thus an underestimation of true cerebral edema in cNWU. The underlying cause remains uncertain but possible cofounders influencing contrast staining in stroke lesions are: kidney function, diagnostic multimodal CT examinations before MT, and the recanalization procedure itself, resulting in different contrast agent preloads. Another already described cofounder to impact cNWU measurements is the time at which the follow-up CT is taken. Lesion hyperattenuations are decreasing in time with up to 84% patients having hyperattenuated lesions directly after MT but only 20% of patients after 24 h (6, 13). Detailed data describing the dynamics of hyperattenuations in acute and subacute stroke lesions are still lacking, and further investigations are needed to determine the temporal relationships.

Our results support previous studies describing NWU in acute stroke lesions as a reliable quantitative imaging biomarker to measure edema in acute stroke lesions (9, 23, 24, 27–29). NWU hereby demonstrates a more accurate quantification of cerebral edema than other methods, such as midline shift measurements, which may significantly depend on age and volume of cerebrospinal fluid (30). This is in accordance with studies showing that NWU is a good predictor of functional outcome and does so more accurately than clinical variables (e.g., NIHSS) or final infarct volume (4–6), while other parameters like ASPECS show low interrater agreement reliability (31). Thus, NWU could serve as an interesting biomarker and imaging end point in stroke trials.

We hypothesized that the densitometric assessment of NWU could be impaired significantly by, even visually inapparent, iodine contrast staining on CP-I after MT, leading to an underestimation of cerebral edema. But the agreement between cNWU and vNWU was high in eight out of 10 patients showing a mean difference of only 2.3%, confirming cNWU and vNWU as a reliable imaging source to quantify NWU.

To our best knowledge, this is the first study to investigate whether residual contrast enhancement affects quantification of NWU in CP-I. As our results demonstrate: contrast staining after MT does not alter the measurement of NWU on CP-I significantly. However, a certain proportion of patients showed a significant difference in NWU between cNWU and vNWU, suggestive to interindividual factors influencing contrast staining.

Designed as a pilot and feasibility study, the number of included patients was small, resulting in low power. Yet, our results confirm previous studies that NWU can be determined reliably on CP-I as well as VNC-I and stimulate future research regarding the potential benefit of VNC-based NWU quantification.

In conclusion, this is the first study to investigate NWU using dual-energy dual-layer CT scans, demonstrating a strong agreement between cNWU and vNWU. Significant differences in cNWU and vNWU are seen in a small subgroup of patients, which should be subject for further research.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical Faculty of the Christian-Albrechts-University, Kiel; Number D 567/18. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

PS, FA, and GB: conceptualization, planning, research, data management, statistical analysis, interpretation of results, and writing. TL: advisor on physical topics. SG: advisor on statistical analysis. JR and TK: help with data aquisition. LM, MB, UH, JF, and OJ: advisor on writing, interpretation of results, and proofreading. All authors contributed to the article and approved the submitted version.

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# The Role of Edema in Subacute Lesion Progression After Treatment of Acute Ischemic Stroke

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**Background:** Ischemic lesions commonly continue to progress even days after treatment, and this lesion growth is associated with unfavorable functional outcome in acute ischemic stroke patients. The aim of this study is to elucidate the role of edema in subacute lesion progression and its influence on unfavorable functional outcome by quantifying net water uptake.

**Methods:** We included all 187 patients from the MR CLEAN trial who had high quality follow-up non-contrast CT at 24 h and 1 week. Using a CT densitometry-based method to calculate the net water uptake, we differentiated total ischemic lesion volume (TILV) into edema volume (EV) and edema-corrected infarct volume (ecIV). We calculated these volumes at 24 h and 1 week after stroke and determined their progression in the subacute period. We assessed the effect of 24-h lesion characteristics on EV and ecIV progression. We evaluated the influence of edema and edema-corrected infarct progression on favorable functional outcome after 90 days (modified Rankin Scale: 0–2) after correcting for potential confounders. Lastly, we compared these volumes between subgroups of patients with and without successful recanalization using the Mann–Whitney *U*-test.

**Results:** Median TILV increased from 37 (IQR: 18–81) ml to 68 (IQR: 30–130) ml between 24 h and 1 week after stroke, while the net water uptake increased from 22 (IQR: 16–26)% to 27 (IQR: 22–32)%. The TILV progression of 20 (8.8–40) ml was mostly caused by ecIV with a median increase of 12 (2.4–21) ml vs. 6.5 (2.7–15) ml of EV progression. Larger TILV, EV, and ecIV volumes at 24 h were all associated with more edema and lesion progression. Edema progression was associated with unfavorable functional outcome [aOR: 0.53 (0.28–0.94) per 10 ml; *p*-value: 0.05], while edema-corrected

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infarct progression showed a similar, non-significant association [aOR: 0.80 (0.62–0.99); *p*-value: 0.06]. Lastly, edema progression was larger in patients without successful recanalization, whereas ecIV progression was comparable between the subgroups.

**Conclusion:** EV increases in evolving ischemic lesions in the period between 1 day and 1 week after acute ischemic stroke. This progression is larger in patients without successful recanalization and is associated with unfavorable functional outcome. However, the extent of edema cannot explain the total expansion of ischemic lesions since edema-corrected infarct progression is larger than the edema progression.

**Keywords: edema, ischemic lesion, infarct, progression, growth, post-treatment, subacute period, acute ischemic stroke**

## INTRODUCTION

Treatment of acute ischemic stroke due to a large vessel occlusion aims to restore the supply of blood to the downstream ischemic tissue and cease the progression of infarction and other pathophysiological processes that result from ischemia (1, 2). Previous studies assessing ischemic and infarcted volumes on computed tomography (CT) and magnetic resonance imaging (MRI) have shown that the ischemic lesion progresses in the subacute period even after (successful) treatment, and this growth is known to be associated with unfavorable functional outcome (1–5). Previous studies have also shown that patients with unsuccessful treatment suffer from more lesion growth compared to those with successful treatment (2). Ischemic lesions as assessed on follow-up non-contrast CT (NCCT) images consist of a combination of infarct and edematous volumes. The lesion evolution may vary based on multiple factors. In patients with unsuccessful or incomplete recanalization, the evolving lesion is expected to predominantly consist of increasing infarct volume, possibly due to the expansion of infarct into the downstream territory caused by persistently reduced blood flow (2). Conversely, in patients with successful recanalization, the evolving lesions may consist of more edematous volume growth as a result of reperfusion injury and status of the microvasculature (6). Distinguishing between infarct and edema volumes (EV) may provide insight on the constituents of subacute lesion growth and help to understand the influence of subacute lesion progression on unfavorable outcome to better target secondary treatments.

Broocks et al. have developed a NCCT densitometry-based technique to quantify edema-related net water uptake within the NCCT lesion (7). In the current study, we aimed to quantify edematous and edema-corrected infarct volumes (ecIV) within the NCCT lesions at 24 h and 1 week after acute ischemic stroke using this net-water uptake based imaging biomarker. With the distinction of EV, we aimed to assess the influence of edema and edema-corrected infarct progression on favorable functional outcome after 90 days. Additionally, we also assessed the influence of successful recanalization and treatment type on edema and edema-corrected infarct progression.

**Abbreviations:** CT, Computed Tomography; MRI, Magnetic Resonance Imaging; NCCT, Non-Contrast Computed Tomography; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; EVT, Endovascular Treatment; IVT, Intravenous Thrombolysis; HU, Hounsfield Unit; HT, Hemorrhagic Transformation; TILV, Total Ischemic Lesion Volume; HV, Hemorrhagic Volume; NWU, Net water uptake; EV, Edema Volume; ecIV, Edema Corrected Infarct Volume; IQR, Inter Quartile Range; mAOL, modified Arterial Occlusion Lesion; NIHSS, NIH Stroke Scale/Score; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; ICA, Intracranial carotid artery; ICA-T, Intracranial carotid artery-T junction; TICI, Thrombolysis in Cerebral Infarction.

## METHODS

### Patient Population

In this study, we included patients that were enrolled in the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial (8). Patients with an acute ischemic stroke due to a large vessel occlusion, above the age of 18 years that could be treated with endovascular treatment (EVT) within 6 h of symptom onset, were randomized to receive intravenous thrombolysis (IVT) with alteplase alone or IVT with alteplase along with EVT. More details regarding the inclusion and exclusion criterion of the trial have been provided in the study protocol (8). The MR CLEAN trial was conducted with the approval of a central medical ethics committee and the research board of each participating center. Patients or their legal representatives provided written informed consent.

The protocol of the MR CLEAN trial required a late follow-up NCCT scan after 1 week (variable time window of ∼3–9 days) of stroke onset to evaluate the final infarct volume. Furthermore, a CT angiography scan was required 24 h after stroke onset to evaluate the post-treatment recanalization status. Performing a NCCT scan along with the CT angiography was common practice. Hence, 280 patients of the MR CLEAN trial received a NCCT scan at both time-points. In the current study, we included patients who underwent NCCT 24 h and 1 week (median: 5, IQR: 5–6 days) after onset of stroke. From these patients, we excluded those that developed a large, diffuse hemorrhages; received hemicraniectomy; or had incomplete images or images with movement artifacts, partial volume artifacts, or other technical and processing errors. From this cohort, we excluded patients with an old infarct on the contralateral hemisphere, whose images had beam hardening artifacts, registration errors, and other

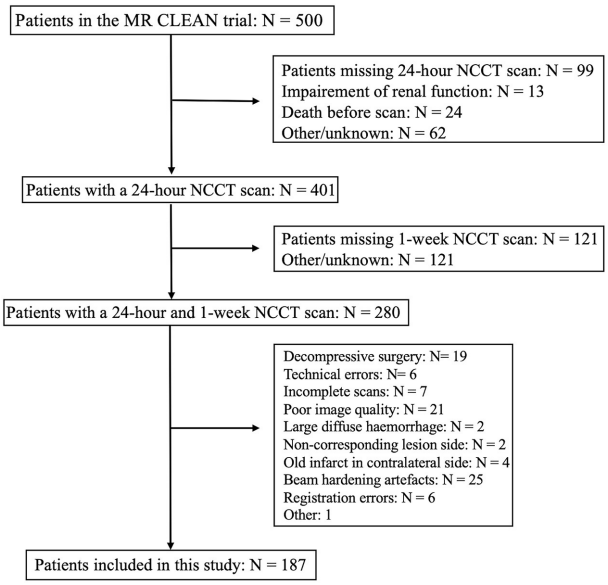


**FIGURE 1 |** Flowchart describing the inclusion and exclusion criterion of this study.

technical issues. **Figure 1** describes the inclusion and exclusion criterion used in this study.

## Image Analysis

### Lesion Assessment

Ischemic lesions on the 24-h NCCT scans were delineated manually on ITK Snap Software with a fixed window width of 30 Hounsfield Units (HUs) and a center-level of 35 HU by two trained observers (4). The lesion delineations included relevant hypodense areas representing edema and/or infarct expanding into the contralateral hemisphere or causing to sulcal and/or ventricular effacement. Hyperdense areas within or surrounding the lesions recognized as hemorrhages or contrast extravasation were also included. Chronic lesions with fluid attenuation, clear borders, and/or without mass effect were not included in the lesion delineation. Only the symptomatic side was revealed to the observers. Ischemic lesions on the 1-week NCCT were automatically segmented using an in-house validated software (9). One of the two experienced neuro-radiologists blinded to the clinical data, except for the symptomatic side, evaluated and corrected the lesions when required. Further details of the lesion assessment have been provided in a previous study (4). Presence of hemorrhagic transformation was assessed by the imaging core lab on the 1-week NCCT scan. The lesion delineations in the patients identified to have hemorrhagic transformations also included hyper-densities representing hemorrhagic transformation in and around the hypodense areas. The hemorrhagic areas were delineated on the 24-h (P.K) and 1-week (K.K) NCCT scans. Regions within the delineation that did not represent hemorrhagic transformation (HT) were identified as non-hemorrhagic regions.

Total ischemic lesion volume (TILV) and hemorrhagic volume (HV) were calculated as the product of number of voxels within the appropriate delineation and the voxel size.

### Net-Water Uptake Quantification

The method developed by Broocks et al. to quantify net-water uptake involves mirroring the lesion to the contralateral hemisphere and calculating the mean density (in HU) of the ipsilateral and contralateral regions-of-interest. To automatically mirror the lesion to the contralateral hemisphere, we used an in-house NCCT atlas with centered, straight head. We first segmented the intracranial region from the 24-h and 1-week NCCT scans to exclude bone, air, and other irrelevant information (10). The segmented intracranial region and the delineated lesions were registered to the in-house atlas using Elastix software and mirrored (11–14). In patients with hemorrhagic transformation, the hemorrhagic region was excluded from the lesion. We selected voxels with a density between 20 and 80 HU from the mirrored segmentations to exclude cerebrospinal fluid and calcifications (7). The mean densities (in HU) in the ipsilateral lesion ($D_{ischemic}$) and in the contralateral segmentation ($D_{normal}$) were calculated. Net water uptake (NWU) per volume of lesion was the defined as (7):

$$NWU = \frac{D_{normal} - D_{ischemic}}{D_{normal}}$$

**Figure 2** displays the steps involved in calculating net water uptake. EV was calculated as the product of the NWU and TILV (in patients without HT) and non-hemorrhagic volume (in patients with HT). ecIV was determined as the difference between TILV, EV, and HV (7). TILV, EV, HV, and ecIV progression were defined as the difference between the 1-week and 24-h TILV, EV HV, and ecIV, respectively.

## Statistical Analysis

TILV, EV, and ecIV (at 24 h and 1 week) and their progression are presented with their median and interquartile range (IQR). We compared the lesion characteristics between 24 h and 1 week using the Wilcoxon signed rank test. We performed exploratory analysis to assess the effect of 24-h lesion characteristics on EV and ecIV progression in the patient population and patient subgroups based on successful recanalization using linear regression analysis. We defined successful recanalization as modified arterial occlusion lesion (mAOL) score of three points evaluated on the 24-h CT angiography scans. Furthermore, we determined the influence of edema and edema-corrected infarct progression on using univariable and multivariable logistic regression analysis, including adjustments for potential confounders. Favorable functional outcome was assessed after 90 days and was defined as modified Rankin Scale 0–2. Baseline, clinical, and imaging and (post) treatment characteristics associated with favorable functional outcome at a significance of $p < 0.1$ were selected as potential confounders. Akaike Information Criterion was used to compare the multivariable logistic regression models with edema and edema-corrected infarct progression. Lastly, to assess the influence of successful recanalization, we compared lesion characteristics between

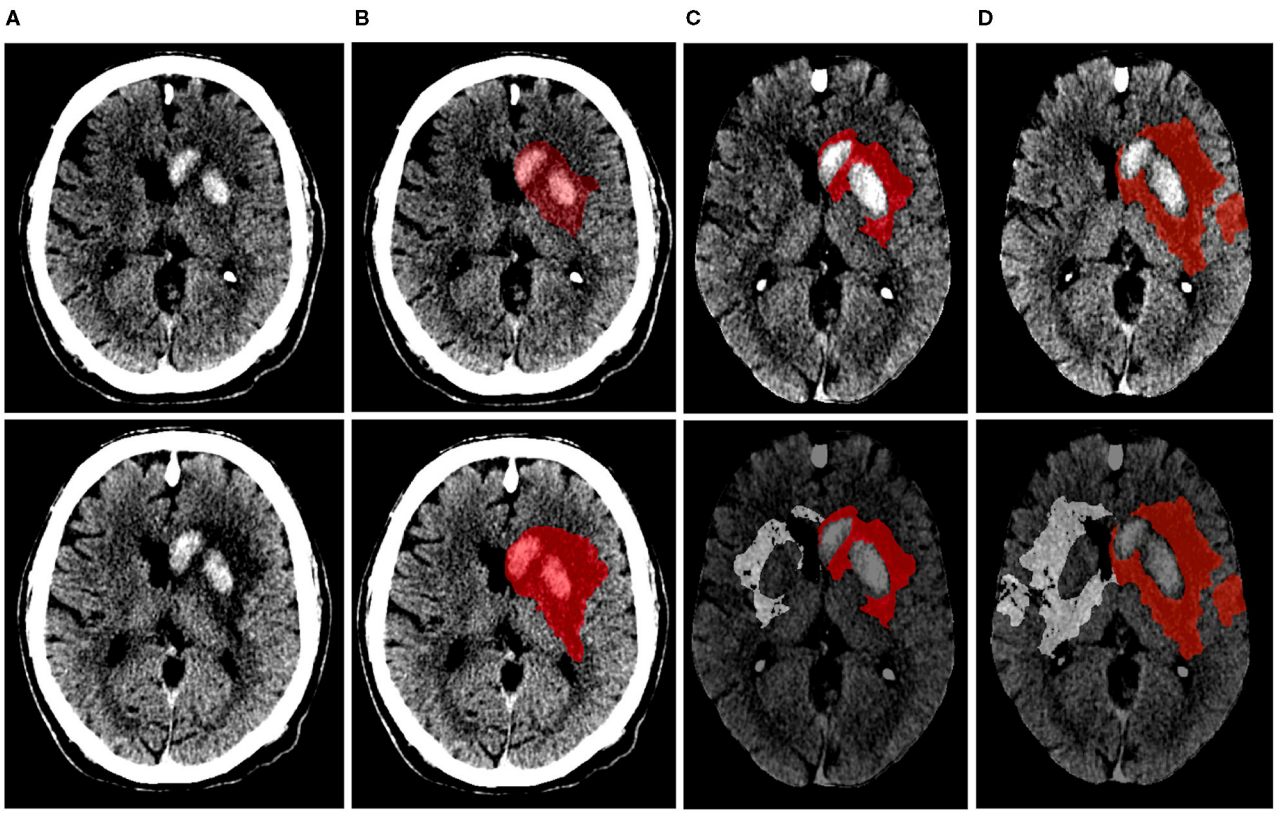


**FIGURE 2 |** Visual representation of the steps involved in calculating net-water uptake on the 24-h (top row) and 1-week (bottom row) NCCT image of the same patient. **(A,B)** show the NCCT image and segmented lesion (represented in red). The NCCT image is registered to an in-house atlas along with the segmented lesion after excluding the hemorrhagic region **(C)**. The lesion is then mirrored to the contra-lateral hemisphere **(D)**. The NWU within the 24-h and 1-week lesion of this patient were 10% and 22%, respectively.

patients that did and did not achieve successful recanalization using the Mann–Whitney *U*-test. The same test was used to assess the influence of EVT on the lesion and lesion progression characteristics.

Dichotomous and categorical baseline, clinical, and treatment characteristics of the study population are presented as proportions; normally distributed continuous variables are presented as mean ± STD and non-normally distributed continuous variables are presented as median and IQR. Patients with missing values were not included in analyses with those particular variables. Statistical analyses were performed using SPSS (IBM SPSS Statistics, version 25, 2018) and R [4.0.2 (2020-06-22) using RStudio Version 1.1.383 – © 2009-2017 RStudio, Inc.]. A $p$-value $\leq 0.05$ was considered statistically significant.

# RESULTS

## Patient Population

Of the 500 patients from the MR CLEAN trial population, we included 187 patients (**Figure 1**). The median age was 66 (IQR: 56–76) years, and 44% of the population was female. The median ASPECTS score was 9 (IQR: 8–10), and median NIHSS at baseline was 17 (IQR: 13–21). Ninety-one (49%) patients were randomized to receive EVT, and 100 (53%) achieved successful recanalization. Information on recanalization status was missing for 16 (8.6%) patients. Baseline characteristics are provided in **Table 1**.

## Lesion Characteristics

In our population, the median TILV after 24 h was 37 (18–81) ml and 1 week was 68 (IQR: 30–130) ml. Median NWU was 22 (IQR: 16–26)% after 24 h and 27 (IQR: 22–32)% 1 week. Wilcoxon signed rank test showed that the TILV, EV, NWU, ecIV, and HV at 24 h were significantly lower than those at 1 week. The median TILV progression was 20 (8.8–40) ml, while the median EV progression and ecIV progression were 6.5 (2.7–15) ml and 12 (2.4–21) ml, respectively. Details of the lesion characteristics are provided in **Table 2**.

## Influence of 24-h Lesion Characteristics on Lesion Progression

In our population, we found that larger EV and ecIV after 24 h were associated with larger edema and TILV progression. Similar trends were also observed in the subgroup of patients with unsuccessful recanalization. However, in the subgroup of patients with successful

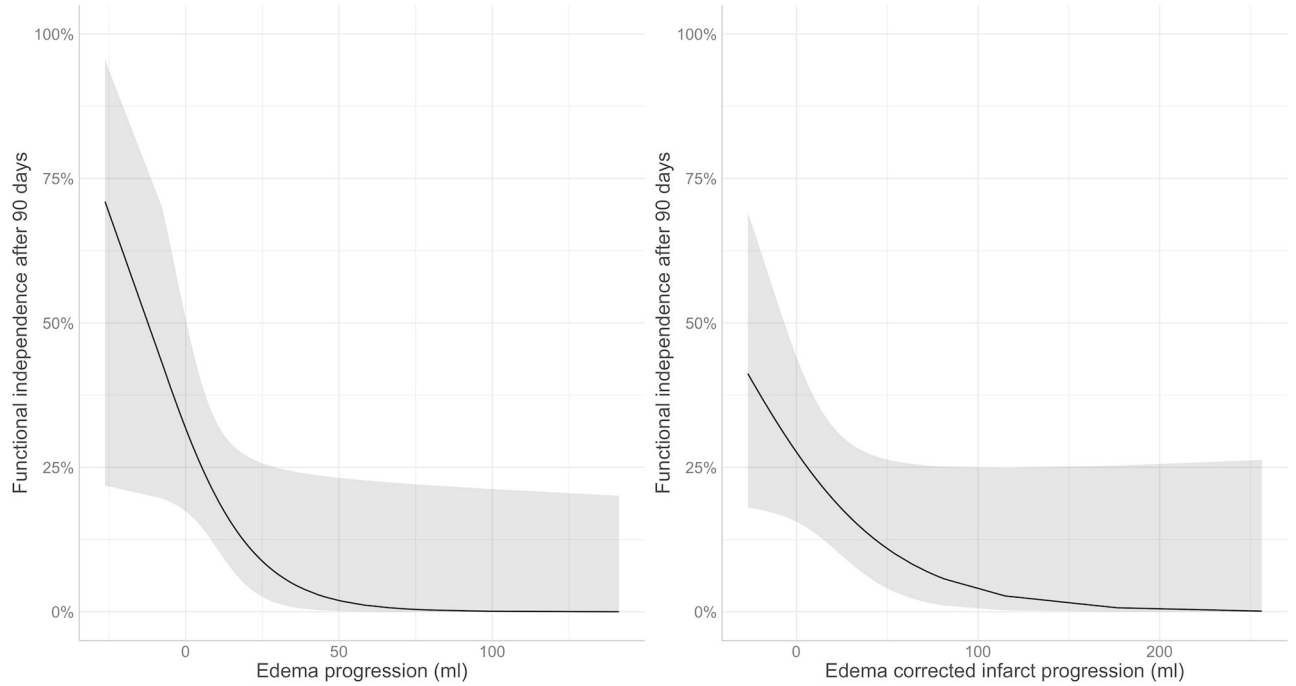


**FIGURE 3 |** Association of post-treatment (left) edema and (right) edema corrected infarct progression in the subacute period with favorable functional outcome (modified Rankin Scale 0–2) after 90 days.

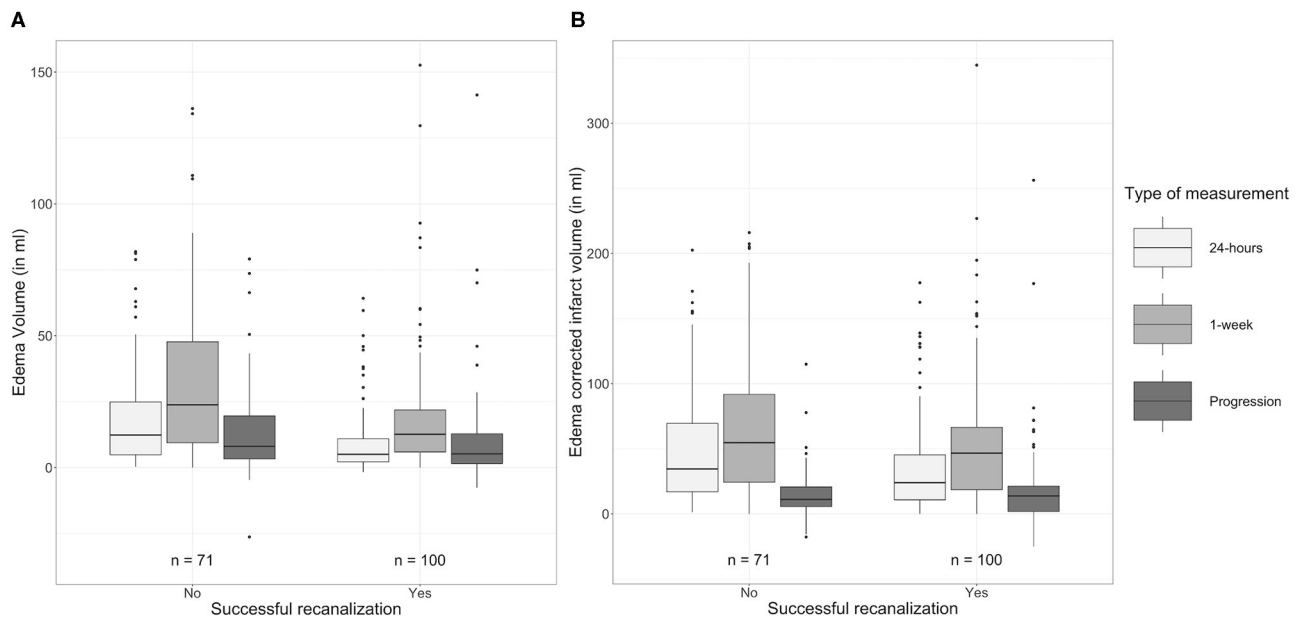


**FIGURE 4 |** Comparison of **(A)** edema volumes and **(B)** edema-corrected infarct volumes after 24 h and 1 week after stroke onset between patients with and without successful recanalization.

recanalization, the association of EV after 24 h with TILV progression was not statistically significant ($p = 0.24$). Details of the univariable linear regression are provided in **Table 3**.

## Influence on Favorable Functional Outcome

Edema and edema-corrected infarct progression were both associated with unfavorable functional outcome in the univariate

**TABLE 1 |** Baseline characteristics of the study population and comparison between patients with and without successful recanalization.

| Variable | | Study population ($n = 187$) | Unsuccessful recanalization ($n = 71$) | Successful recanalization ($n = 100$) | $p$-value |
|---|---|---|---|---|---|
| Age (in years) | | 66 (56–76) | 62 (51–73) | 67 (57–76) | 0.06 |
| Male sex | | 104 (56%) | 43 (61%) | 55 (55%) | 0.57 |
| Previous ischemic stroke | | 13 (7.0%) | 3 (4.2%) | 10 (10%) | 0.27 |
| Myocardial infarction | | 23 (12%) | 11 (15%) | 11 (11%) | 0.53 |
| Diabetes mellitus | | 18 (9.6%) | 6 (8.5%) | 8 (8%) | 1 |
| Hypertension | | 94 (50%) | 32 (45%) | 52 (52%) | 0.46 |
| Atrial fibrillation | | 53 (28%) | 17 (24%) | 29 (29%) | 0.58 |
| Hypercholesterolemia | | 44 (24%) | 15 (21%) | 24 (24%) | 0.80 |
| Current smoking | | 57 (30%) | 24 (34%) | 31 (31%) | 0.83 |
| Antiplatelet drugs | | 53 (28%) | 20 (28%) | 28 (28%) | 1 |
| Coumarins | | 12 (6.4%) | 1 (1.4%) | 8 (8%) | 0.08 |
| Statins | | 54 (29%) | 18 (25%) | 30 (30%) | 0.62 |
| Anti-hypertensive drugs | | 98 (52%) | 33 (46%) | 54 (54%) | 0.42 |
| Systolic blood pressure (mmHg) | | 140 (125–160) | 139 (125–160) | 140 (126–158) | 0.64 |
| Clinical hemisphere side left | | 105 (56%) | 42 (59%) | 52 (52%) | 0.44 |
| Pre-stroke modified Rankin Scale (0–2) | | 177 (95%) | 68 (96%) | 94 (94%) | 0.74 |
| Baseline NIHSS | | 17 (13–21) | 17 (13–21) | 17 (13–21) | 0.91 |
| Proximal occlusion (ICA or ICA-T) | | 50 (27%) | 20 (28%) | 26 (26%) | 0.89 |
| ASPECTS score | Summary | 9 (8–10) | 9 (8–10) | 9 (8–10) | 0.51 |
| | Missing | 2 (1.1%) | | | |
| Collateral score | Absent | 4 (2.2%) | 1 (1.4%) | 2 (2.0%) | 0.19 |
| | Filling <50% of the occluded area | 51 (27%) | 13 (18%) | 32 (32%) | |
| | Filling >50% and <100% of the occluded area | 69 (37%) | 31 (44%) | 33 (33%) | |
| | Filling 100% of the occluded area | 62 (33%) | 26 (37%) | 32 (32%) | |
| | Missing | 1 (0.54%) | | | |
| Received iv thrombolysis | | 169 (90%) | 66 (93%) | 89 (89%) | 0.54 |
| Allocated to endovascular treatment | | 91 (49%) | 15 (21%) | 69 (69%) | <0.01 |
| Time to randomize (minutes) | | 190 (150–260) | 200 (150–270) | 190 (150–250) | 0.12 |

*Data are displayed as median (interquartile range) or number (percentage of population). Mann–Whitney U-test and Chi-Square/Fisher-tests were performed to compare continuous and binary/categorical variables between the successful and unsuccessful recanalization sub-groups, appropriately.*

analysis [OR: 0.40 (0.24–0.60); $p$-value: <0.01; OR: 0.76 (0.62–0.91) per 10 ml; $p$-value: <0.01]. Similar results with slightly lower significance levels were observed in the multivariable analysis including adjustments for potential confounders [aOR: 0.53 (0.28–0.94) $p$-value: 0.05; aOR: 0.80 (0.62–0.99); $p$-value: 0.06] for 10 ml of EV and ecIV progression, respectively (**Figure 3**). The AIC of the multivariable model with edema progression (181.5) and edema-corrected infarct progression (181.8) were comparable. Details of the multivariable logistic regression are provided in **Table 4**.

## Influence of Treatment

As shown in **Table 5** and **Figure 4**, patients with successful recanalization had significantly lower TILV ($p = 0.02$), EV ($p < 0.01$), and ecIV ($p = 0.03$) after 24 h compared to those without successful recanalization. Patients with successful recanalization had lower EV ($p < 0.01$) and non-significantly different ecIVs ($p = 0.11$) after 1 week. Furthermore, edema progression ($p = 0.01$) was lower in patients with successful recanalization compared to those without successful recanalization, while the ecIV progression was comparable between the subgroups ($p = 1.00$).

Patients randomized to receive EVT had lower EV and percentages of NWU after 24 h ($p = 0.01$; $p < 0.01$, respectively) and lower NWU after 1 week ($p = 0.03$) compared to those who did not receive EVT. Details of the lesion characteristics compared between patients that did and did not receive EVT are provided in **Table 6**.

# DISCUSSION

In this study, we showed that EV, ecIV, and hemorrhage volume continue to progress after 24 h and that larger lesions after 24 h are associated with more lesion progression in the subacute

**TABLE 2 |** Ischemic lesion characteristics obtained in the subacute period after treatment in 187 patients.

| Type of measurement | 24 h | 1 week | Progression | *p*-value |
|---|---|---|---|---|
| Total ischemic lesion volume (ml) | 37 (18–81) | 68 (30–130) | 20 (8.8–40) | <0.01** |
| Net water uptake (%) | 22 (16–26) | 27 (22–32) | 6.0 (0.33–11) | <0.01** |
| Edema volume (ml) | 7.5 (2.9–17) | 15 (7.9–35) | 6.5 (2.7–15) | <0.01** |
| Edema corrected infarct volume (ml) | 29 (15–62) | 51 (21–87) | 12 (2.4–21) | <0.01** |
| Hemorrhage volume (ml) | 0 (0–1.3) | 0 (0–2.4) | 0 (0–0) | 0.04* |

*All data are displayed as median (interquartile range). Wilcoxon signed rank-test was performed between lesion characteristics obtained after 24 h and 1 week.*
***$p \leq 0.01$.*
**$p \leq 0.05$.*

**TABLE 3 |** Univariable linear regression of the 24-h ischemic lesion characteristics and edema, edema-corrected infarct and lesion volume progression in the subacute period.

| Measurement | Population ß (95% CI) *n* = 188 | Unsuccessful recanalization ß (95% CI) *n* = 71 | Successful recanalization ß (95% CI) *n* = 100 |
|---|---|---|---|
| **Independent variable—Edema progression (ml)** | | | |
| Edema volume (ml) | 0.37 (0.21–0.52)** | 0.35 (0.17–0.53)** | 0.39 (0.12–0.65)** |
| Edema corrected infarct volume (ml) | 0.22 (0.17–0.27)** | 0.23 (0.16–0.3)** | 0.19 (0.1–0.27)** |
| Total ischemic lesion volume (ml) | 0.15 (0.11–0.19)** | 0.15 (0.1–0.2)** | 0.13 (0.06–0.19)** |
| **Independent variable—Edema corrected infarct progression (ml)** | | | |
| Edema volume (ml) | 0.05 (−0.19–0.3) | 0.15 (−0.08–0.38) | 0.07 (−0.46–0.60) |
| Edema corrected infarct volume (ml) | 0.06 (−0.03–0.16) | 0.1 (0–0.2)* | 0.12 (−0.06–0.3) |
| Total ischemic lesion volume (ml) | 0.04 (−0.03–0.11) | 0.06 (−0.01–0.13)$^{\S}$ | 0.07 (−0.06–0.2) |
| **Independent variable—Lesion progression (ml)** | | | |
| Edema volume(ml) | 0.41 (0.05–0.78)* | 0.49 (0.14–0.85)** | 0.45 (−0.3–1.2) |
| Edema corrected infarct volume (ml) | 0.28 (0.15–0.42)** | 0.32 (0.18–0.47)** | 0.31 (0.06–0.56)* |
| Total ischemic lesion volume (ml) | 0.18 (0.09–0.28)** | 0.21 (0.1–0.31)** | 0.2 (0.02–0.38)* |

***$p \leq 0.01$.*
**$p \leq 0.05$.*
*$^{\S}p \leq 0.10$.*

period. Furthermore, we showed that edema progression is associated with unfavorable functional outcome and that it is lower in patients who have successful recanalization.

To our knowledge, this is the first study to quantify edema progression in ischemic lesions assessed in the subacute period after stroke onset. EVs are generally described using indirect and global imaging markers like midline shift—the gold standard for assessing edema, and hemispheric, lateral ventricular, or swelling volume (15–17). Broocks et al. have developed a densitometry based NWU measure that relies on the relationship of increasing lesion volume due to water content and the associated density reduction on NCCT (18). Due to the increased reliability to distinguish EV from within the ischemic lesion compared to the global imaging markers and its easy applicability to widely available NCCT scans, this method was utilized in this study (7, 19–21).

The 24-h NWU observed in this study (22%) is comparable with the 24-h NWU presented in a previous study (20.6%) (7). We extended this finding and showed that NWU, edema, and ecIV are significantly larger after 1 week compared to those assessed 24 h after stroke onset. This indicates that the lesion progresses due to an increase in both edematous and true-infarct volumes. Ischemia and post-ischemic reperfusion deteriorate the integrity of the capillaries in the blood brain barrier, leading to more edema and ischemia. The cascading effect of the increased EV and associated rise in tissue pressure results in an increase in the mechanical forces experienced by the surrounding tissue, ultimately increasing edema and lesion volumes (22). This is supported by our finding that larger 24-h edema, edema corrected infarct, and the total lesion volume are associated with larger subacute edema and lesion progression. In this study, we calculated EV using a densitometry-based technique that measures the water content within the ischemic lesion. Hence, the EVs estimated in this study could be a marker for vasogenic edema, and not cytotoxic edema occurring due to osmotic gradients between the extra and intra-cellular spaces (22). Thus, the ecIVs are a marker for true infarct tissue, cytotoxic edema, and other ischemic components that cannot be distinguished on NCCT scans. Furthermore, we did not find that the 24-h lesion characteristics influence edema-corrected infarct progression. This may indicate that edema corrected infarct mainly extends into the downstream at-risk territory. It is also possible

**TABLE 4 |** Multivariable logistic regression analysis of edema and edema-corrected infarct progression with favorable functional outcome (modified Rankin Scale 0–2) in 187 patients.

| Variable | Model 1: Edema progression | | Model 2: Edema corrected infarct progression | |
|---|---|---|---|---|
| | Odds ratio (95% CI) | *p*-value | Odds ratio (95% CI) | *p*-value |
| Progression^ | 0.53 (0.28–0.94) | 0.05* | 0.80 (0.62–0.99) | 0.06ϕ |
| Total ischemic lesion volume^ | 0.83 (0.72–0.94) | 0.01** | 0.79 (0.69–0.89) | <0.01** |
| Age | 0.96 (0.93–0.99) | 0.01** | 0.96 (0.93–0.99) | 0.01** |
| Coumarines | 0.12 (0–1.10) | 0.11 | 0.12 (0–1.07) | 0.11 |
| Systolic blood pressure | 0.99 (0.97–1.01) | 0.26 | 0.99 (0.97–1.01) | 0.23 |
| Baseline NIHSS | 0.94 (0.87–1.00) | 0.07ϕ | 0.94 (0.88–1.01) | 0.10ϕ |
| Proximal occlusion | 0.42 (0.15–1.07) | 0.08ϕ | 0.38 (0.14–0.99) | 0.06ϕ |
| Collaterals | 1.03 (0.59–1.77) | 0.92 | 0.94 (0.54–1.61) | 0.82 |
| Intra-arterial thrombectomy | 2.29 (1.06–5.06) | 0.04* | 2.29 (1.06–5.06) | 0.04* |

^*Analysis done for 10 ml volume.*
***p ≤ 0.01.*
**p ≤ 0.05.*
*ϕp ≤ 0.10.*

**TABLE 5 |** Comparison of ischemic lesion characteristics obtained in the subacute period after treatment in patients with and without successful recanalization.

| | 24 h | | | 1 week | | | Progression | | |
|---|---|---|---|---|---|---|---|---|---|
| **Successful recanalization** | **No (*n* = 71)** | **Yes (*n* = 100)** | ***p*-value** | **No (*n* = 71)** | **Yes (*n* = 100)** | ***p*-value** | **No (*n* = 71)** | **Yes (*n* = 100)** | ***p*-value** |
| Total ischemic lesion volume (ml) | 54 (23–98) | 33 (13–62) | 0.02* | 81 (35–140) | 63 (24–97) | 0.06 | 22 (10–43) | 19 (5.4–33) | 0.33 |
| Edema volume (ml) | 12 (4.9–25) | 5.1 (2.2–11) | <0.01** | 24 (9.4–48) | 13 (5.9–22) | <0.01** | 8.0 (3.3–20) | 5.2 (1.6–13) | 0.01* |
| Net water uptake (%) | 24 (21–28) | 20 (14–24) | <0.01** | 30 (25–35) | 25 (20–29) | <0.01** | 5.6 (0.19–11) | 6.0 (−0.04–11) | 0.86 |
| Edema corrected infarct volumes (ml) | 34 (17–69) | 24 (11–45) | 0.03* | 55 (24–92) | 47 (19–66) | 0.11 | 11 (5.7–21) | 14 (1.9–21) | 1.00 |
| Hemorrhage volume (ml) | 0 (0–1.1) | 0 (0–1.3) | 0.77 | 0 (0–2.1) | 0 (0–1.8) | 0.66 | 0 (0–0.0) | 0 (0–0) | 0.80 |

*All data are displayed as median (interquartile range). Mann–Whitney U-test was performed to assess differences in lesion characteristics between patients with and without successful recanalization (mAOL = 3 points).*
***p ≤ 0.01.*
**p ≤ 0.05.*

that edema-corrected infarct progression could be caused by other factors such as unsuccessful recanalization, no-reflow phenomenon, thrombus fragmentation, and/or formation of microvascular emboli (6). This could be supported by our finding that the 24-h lesion characteristics only showed a similar trend in the sub-population of unsuccessful recanalization. Nevertheless, the mechanism of edema-corrected infarct progression still needs to be explored.

In a previous study on this patient population, we showed that lesion progression in the subacute period is associated with unfavorable functional outcome (5). In the current study, we extended this finding to show that edema progression within the lesion is associated with unfavorable functional outcome. This finding is in line with previous studies that assessed the influence of edema on functional outcome (15, 23, 24). It is surprising that in our population, edema-corrected infarct progression only showed a similar but non-significant trend that could be due to the overlapping effect of adjusting for the 24-h lesion volume. However, due to the pertinent association between infarct and edema, a similar study on a larger population is required to validate our findings.

Successful recanalization is known to decrease edema formation. Kimberly et al. showed reduced edema, defined by midline shift, on early follow-up (24 h) and late follow-up (5–7 days) in patients with successful recanalization (15). Similarly, Broocks et al. showed that patients with successful treatment, defined as reperfusion using TICI score, have decreased NWU and associated EVs after 24 h compared to those with unsuccessful treatment (21). In addition to showing comparable results after 24 h, we showed that the similar trend

**TABLE 6 |** Comparison of ischemic lesion characteristics obtained in the subacute period after treatment in patients that were randomized to receive EVT and iVT or only IVT.

| | 24 h | | | 1 week | | | Progression | | |
|---|---|---|---|---|---|---|---|---|---|
| **iVT + EVT** | **No** ***N*= 96** | **Yes** ***N* = 91** | ***p*-value** | **No** ***N* = 96** | **Yes** ***N* = 91** | ***p*-value** | **No** ***N* = 96** | **Yes** ***N* = 91** | ***p*-value** |
| Total ischemic lesion volume (ml) | 48 (23–81) | 33 (16–77) | 0.10 | 79 (35–130) | 58 (25–99) | 0.12 | 21 (11–43) | 20 (6.8–35) | 0.26 |
| Edema volume (ml) | 8.8 (5.0–20) | 4.7 (2.1–13) | 0.01** | 20 (9.5–39) | 14 (6.0–27) | 0.07 | 6.7 (2.9–17) | 6.1 (2.0–14) | 0.36 |
| Percentage NWU | 23 (18–28) | 21 (14–24) | <0.01** | 28 (23–33) | 26 (21–30) | 0.03* | 5.3 (−0.30–10) | 7.0 (1.1–12) | 0.15 |
| Edema corrected infarct volume (ml) | 35 (17–64) | 23 (13–56) | 0.14 | 55 (25–93) | 41 (19–73) | 0.20 | 12 (5.3–22) | 12 (1.7–21) | 0.32 |
| Hemorrhage volume (ml) | 0 (0–0.86) | 0 (0–2.3) | 0.79 | 0 (0–2.6) | 0 (0–1.6) | 0.99 | 0 (0–0.49) | 0 (0–0) | 0.07 |

*All data are displayed as median (interquartile range). Mann–Whitney U-test was performed to assess differences in lesion characteristics between patients with and without EVT.*
***$p \leq 0.01$.*
**$p \leq 0.05$.*

continues in the subacute period up to 1 week after onset. Patients with successful recanalization demonstrated reduced EVs in comparison with patients that do not have successful recanalization in the late follow-up images as well. Furthermore, Broocks et al. also showed that growth of lesion and edema corrected infarct is lower in patients with successful treatment compared to those without successful treatment (7). Moreover, Federau et al. assessed ischemic lesions on MR perfusion images in the subacute period and showed reduced subacute lesion growth in patients that have >90% reperfusion (2). In our population, we observed similar trends in lesion and ecIVs after 24 h. We observed that total lesion and ecIV at 1 week, and lesion progression was lower in patients that have successful recanalization; however, these differences were not statistically significant. Furthermore, our finding that patients that received EVT presented with lower NWU after 24 h and 1 week further establishes the benefit of iVT and EVT over iVT only.

Our study has a few limitations. Firstly, as the 1-week NCCT scans were obtained between approximately 3 and 9 days, and since it is known that the influence of edema is most pronounced in the subacute period after stroke onset, future studies assessing the bias of the variable time frame on lesion and growth of its constituents are required (4). Secondly, mTICI score assessed on digital subtraction angiography (DSA) scans is the standard measure for reperfusion and treatment success. However, in this study, treatment success was defined as recanalization status using the mAOL score assessed on the 24-h CTA scans since DSAs were only available for the patients randomized to receive IVT and EVT. There can be a difference in the recanalization directly assessed after EVT using DSA images and assessed 24-h after treatment because of the dynamic behavior of clot formation and dissolution. Therefore, our results cannot directly be translated to current measures of treatment success. Thirdly, hyper-densities within the hypodense areas recognized as hemorrhage or contrast extravasation were included in the lesion delineations. However, hemorrhagic regions within these lesions were only defined for patients identified to be suffering from hemorrhagic transformation on the 1-week scan. Thus, the net water uptake measurements could have been biased by the influence of contrast extravasation. Lastly, 24-h lesion volume was as a potential confounder in the multivariable regression model to assess the influence of edema progression on favorable functional outcome despite being significantly associated with edema progression. This could have led to some errors associated with multicollinearity. However, since the purpose was to assess the influence of edema progression, after accounting for the TILV after 24 h, on functional outcome, both these variables were of interest and included in the final model.

## CONCLUSION

Both edema and ecIVs continue to progress in the subacute period after treatment of stroke, noting that lesion progression cannot be explained by increase in edema alone. Edema progression is associated with unfavorable functional outcome and is larger in patients with unsuccessful recanalization and in patients with large 24-h infarct lesions. This could also help in improving the identification of secondary treatment targets for subacute care of patients after an acute ischemic stroke.

## DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available due to ethical restrictions that prevent the sharing of patient data. Requests to access the datasets should be directed to the MR CLEAN executive committee (www.mrclean-trial.org), mrclean@erasmusmc.nl.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by a Central Medical Ethics Committee and the research boards of all participating centers accepted the MR CLEAN trial. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

WZ, AL, RO, DD, YR, and CM designed the MR CLEAN trial. OB collected and prepared the data for the trial. PK, KK, OB, and AB prepared data for this study. PK performed the statistical analysis, interpreted the results, and drafted the paper. HM assisted with the statistical analysis, interpretation of the results, and drafting the paper. KK, AB, KT, OB, AY, WZ, RO, AL, DD, YR, JB, and CM critically revised the paper. All authors contributed to the article and approved the submitted version.

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# Pretreatment of Sulfonylureas Reducing Perihematomal Edema in Diabetic Patients With Basal Ganglia Hemorrhage: A Retrospective Case-Control Study

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**Background:** The sulfonylurea receptor 1–transient receptor potential melastatin 4 (SUR1–TRPM4) channel is a target key mediator of brain edema. Sulfonylureas (SFUs) are blockers of the SUR1–TRPM4 channel. We made two assessments for the pretreatment of SFUs: (1) whether it associates with lower perihematomal edema (PHE) and (2) whether it associates with improved clinical outcomes in diabetic patients who have acute basal ganglia hemorrhage.

**Methods:** This retrospective case-control study was conducted in diabetic adults receiving regular SFUs before the onset of intracerebral hemorrhage (ICH). All of the patients received the clinical diagnosis of spontaneous basal ganglia hemorrhage. The diagnosis was confirmed by a CT scan within 7 days after hemorrhage. For each case, we selected two matched controls with basal ganglia hemorrhage based on admission time (≤5 years) and age differences (≤5 years), with the same gender and similar hematoma volume. The primary outcome was PHE volume, and the secondary outcomes were relative PHE (rPHE), functional independence according to modified Rankin Scale score and Barthel Index at discharge, and death rate in the hospital.

**Results:** A total of 27 patients (nine cases and 18 matched controls), admitted between January 1, 2009 and October 31, 2018, were included in our study. There was no significant association between SFU patients and non-SFU patients on PHE volumes [15.4 (7.4–50.2 ml) vs. 8.0 (3.1–22.1) ml, $p = 0.100$]. Compared to non-SFU patients, the SFU patients had significantly lower rPHE [0.8 (0.7–1.3) vs. 1.5 (1.2–1.9), $p = 0.006$]. After we adjusted the confounding factors, we found that sulfonylureas can significantly reduce both PHE volume (regression coefficient: −13.607, 95% CI: −26.185 to −1.029, $p = 0.035$) and rPHE (regression coefficient: −0.566, 95% CI: −0.971 to −0.161, $p = 0.009$). However, we found no significant improvement in clinical outcomes at discharge, in the event of pretreatment of SFUs before the onset of ICH, even after we adjusted the confounding factors.

**Conclusion:** For diabetic patients with acute basal ganglia hemorrhage, pretreatment of sulfonylureas may associate with lower PHE and relative PHE on admission. No significant effect was found on the clinical outcomes when the patients were discharged. Future studies are needed to assess the potential clinical benefits using sulfonylureas for ICH patients.

**Keywords: sulfonylureas, perihematomal edema, intracerebral hemorrhage, prognosis, case-control study**

# INTRODUCTION

Intracerebral hemorrhage (ICH) accounts for 10% of all strokes. It is associated with high disability and mortality risks; therefore, it brings a huge burden to the society today (1). The physical effects of hematoma (mass effect) and secondary perihematomal edema (PHE) are major causes of severe neurological deficits and even death. Although symptomatic treatments, such as osmotic drugs, have been used on ICH patients, their therapeutic effects are insufficient. Therefore, the need for novel anti-edema drugs has become more urgent (2).

Among all mechanisms causing brain edema, blood-brain barrier hyperpermeability and cell swelling inducers have been the two main foci (2). Out of all the target mediators, a key potential candidate is the sulfonylurea receptor 1–transient receptor potential melastatin 4 (SUR1–TRPM4) channel. In response to the depletion of ATP by hypoxia, the SUR1–TRPM4 channel opens and releases an unregulated flow of ions and therefore causes brain edema (3). In rodent stroke models, sulfonylureas were confirmed as a blocker to the SUR1–TRPM4 channel. They reduce non-selective ion influx and excess brain water in peri-infarct regions (3). Recently, clinical trials suggested that, after an ischemic stroke, sulfonylureas reduce symptomatic hemorrhagic transformation (4, 5). Besides this, pretreated sulfonylureas were associated with smaller volumes of hematoma and PHE after ICH as well as improved discharge destination (6, 7).

Basal ganglia hemorrhage, the most common form of spontaneous ICH, is associated with a high mortality risk (8). In this study, we investigated the effects of sulfonylureas pretreatment on volumes of PHE on admission and clinical outcomes at discharge for diabetic patients with basal ganglia hemorrhage.

# MATERIALS AND METHODS

## Patients and Data Collection

We conducted a retrospective case-control study of diabetic patients with acute ICH admitted at the Department of Neurology of the Xijing Hospital of Air Force Medical University, Xi'an, China, from January 1, 2009 to October 31, 2018. The patients included in the study were over 18 years old, had sulfonylureas before the onset, and were diagnosed as spontaneous basal ganglia hemorrhage as confirmed by computed tomography (CT) scan within the first 7 days. For each case, two matched controls with basal ganglia hemorrhage were selected based on the most recent admission data ($\leq$5 years), with age difference within 5 years, the same gender, and similar hematoma volume. The patients were excluded if they had a modified Rankin Scale (mRS) score $\geq$3, they had a secondary ICH, or the cranial CT was unavailable upon admission. Midline shift was measured as the perpendicular distance between the septum pellucidum and the ideal midline (the line being coplanar with the falx cerebri) (9). The primary outcome was PHE volume, and the secondary outcomes were relative PHE (rPHE, a ratio of PHE to ICH volume), functional independence according to mRS score and Barthel Index at discharge, and death rate in the hospital. This study was approved by the Ethics Committee of Xijing Hospital (KY20182067-F-1). Given that this study was retrospective, informed consent was not available.

## Imaging Analysis

An independent neuroradiologist blindly measured the ICH and PHE volumes using the 3D slicer software (v.4.10.2; NIH US) based on the regions of interest from the head CT of the patients upon admission. The assessment of the evaluating agreement of the researchers was performed in another study from our group, and the results indicated a high agreement for our researchers (10). In addition, the volume of ICH and PHE on CT was measured using a semiautomatic volumetric algorithm in our study (11). rPHE was calculated using the following formula: rPHE = PHE volume/ICH volume.

## Statistical Analysis

The statistical analysis was completed using the Statistical Package for Social Science (version 19.0 for Windows; SPSS Inc., Chicago). Normally distributed data were described as mean (standard deviation) and analyzed by Student's t-test. Skewed data were described as median (interquartile range) and analyzed by Mann–Whitney U-test. Chi-square test or Fisher exact test was used for comparison between dichotomous data. Linear regression or binary logistic regression were performed for multivariate analysis. Statistical significance was set as a two-sided $P < 0.05$.

# RESULTS

## Study Population

A flow diagram of the included and excluded patients is provided in **Figure 1**. From January 1, 2009 to October 31, 2018, a total of 1,835 patients with spontaneous ICH were admitted to Xijing Hospital. Among them, 146 diabetic patients met the criteria of this study, which required ICH in the basal ganglia region. Nine patients pretreated with sulfonylureas before the onset of

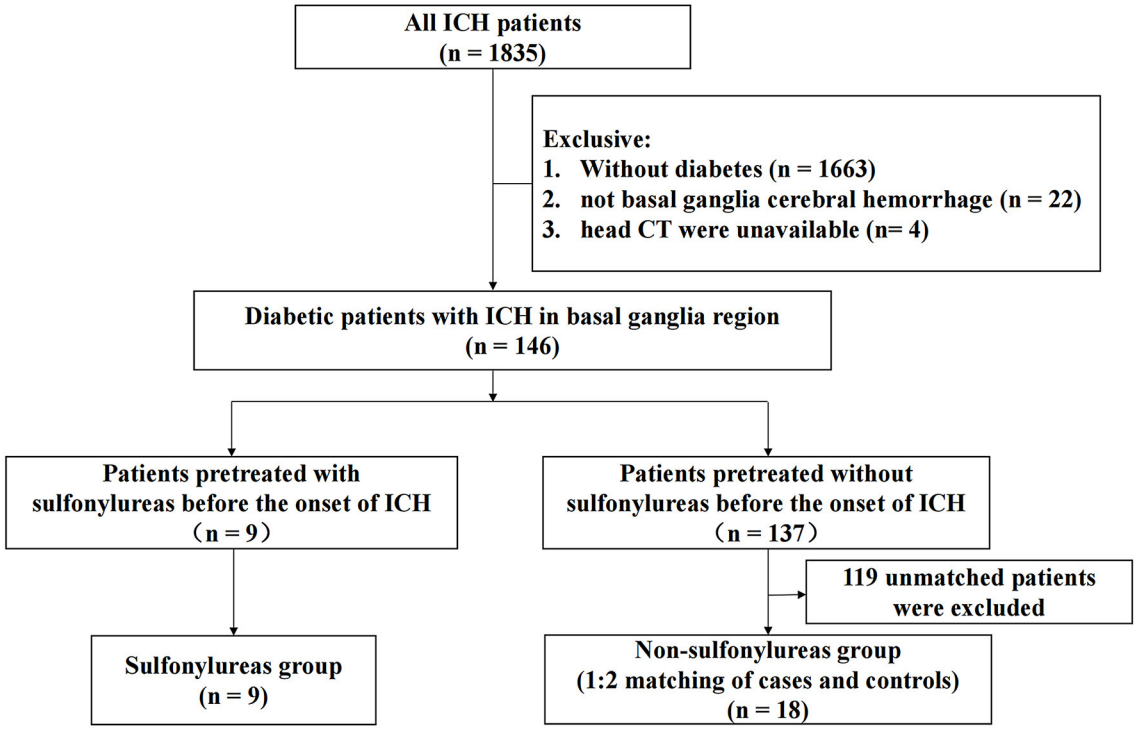


**FIGURE 1 |** Flow diagram of the included and excluded patients.

ICH were included in the sulfonylureas group (SFU patients), and 18 matched controls were selected (non-SFU patients). The average onset age of patients was 61 (51–71) years old. Out of all patients, 77.8% were male, and the average clinical scores were as follows: the NIHSS score was 13.0 (5.0–36.0), the Glasgow Coma Score (GCS) score was 14.0 (6.0–15.0), and the ICH score was 1.0 (0.0–3.0). The two groups did not differ significantly in baseline characteristics, such as age, gender, past history, medication history, blood pressure, clinical scores, and laboratory indicators, upon admission. The only major difference was that the time from onset to admission head CT in the sulfonylureas group was longer than that in the non-sulfonylureas group [1 (1–3) vs. 1 (1–1) days, $P = 0.011$] (**Table 1**). The clinical characteristics are shown in **Table 1**.

## Treatment During Hospitalization

During hospitalization, more than half of the SFU patients continued to use sulfonylureas for blood glucose control, with a significantly higher rate than those in the non-SFU group (55.6 vs. 5.6%, $P = 0.008$). Between the two groups, there was no statistical difference in the treatment for blood pressure control nor in the use of osmotic drugs, hemostasis, craniotomy, drainage, mechanical ventilation, or other treatments.

## Imaging Characteristics

The measurements of hematoma and PHE using 3D slicer software package is provided in **Figure 2**. We found that there was no significant association between SFU patients and non-SFU patients on PHE volume [15.4 (7.4–50.2) ml vs. 8.0 (3.1–22.1) ml, $p = 0.100$]. However, the rPHE in SFU patients was significantly lower [0.8 (0.7–1.3) vs. 1.5 (1.2–1.9), $p = 0.006$], while there was no significant difference between the two groups in hematoma breaking into ventricles and midline shift. **Table 2** shows the results of the first head CT upon admission of the SFU and non-SFU patients.

In order to clarify the influence of confounding factors on our results, we carried out collinearity statistics in regression analysis. The results showed that there was no multicollinearity in the regression analysis in our study (**Table 3**). After adjusting for confounding factors, we found that sulfonylureas significantly associated with a lower PHE volume (regression coefficient: −13.607, 95% CI: −26.185 to −1.029, $p = 0.035$) and rPHE (regression coefficient: −0.566, 95% CI: −0.971 to −0.161, $p = 0.009$) (**Table 4**).

## Clinical Outcomes

The average mRS score was 4 at the time the patients were discharged in both groups; no significant differences were found ($P = 0.831$). In neither group did we find any significant association between pretreatment of sulfonylureas and in-hospital mortality, the number of patients with mRS $\geq$ 3, or Barthel Index at discharge. This remained true even after we adjusted for confounding factors (age, gender, NIHSS and GCS on admission, imaging data including ICH volume, PHE volume, hematoma breaking into ventricles and midline shift, and sulfonylureas during hospitalization).

**TABLE 1 |** Baseline characteristics of sulfonylureas (SFU) and non-SFU patients.

| | All patients (*N* = 27) | Non-SFU patients (*N* = 18) | SFU patients (*N* = 9) | *P*-value |
|---|---|---|---|---|
| Age (years) | 61 (51–71) | 61 (51–68) | 61 (45–72) | 0.837 |
| Male (*N*, %) | 21 (77.8%) | 14 (77.8%) | 7 (77.8%) | 1.000 |
| Time from onset to admission head CT (day)[a] | 1 (1–1) | 1 (1–1) | 1 (1–3) | 0.011 |
| ICH volume (ml) | 11.4 (4.24–31.94) | 12.7 (5.0–36.3) | 11.4 (3.0–30.8) | 0.440 |
| **Past history** | | | | |
| Stroke (*N*, %) | 4 (14.8%) | 4 (22.2%) | 0 (0.0%) | 0.268 |
| Hypertension (*N*, %) | 20 (74.1%) | 13 (72.2%) | 7 (77.8%) | 1.000 |
| Coronary heart disease (*N*, %) | 3 (11.1%) | 1 (5.6%) | 2 (22.2%) | 0.250 |
| Hyperlipidemia (*N*, %) | 2 (7.4%) | 1 (5.6%) | 1 (11.1%) | 1.000 |
| Alcoholism (*N*, %) | 2 (7.4%) | 1 (5.6%) | 1 (11.1%) | 1.000 |
| Smoking (*N*, %) | 6 (22.2%) | 2 (11.1%) | 4 (44.4%) | 0.136 |
| **Medication history** | | | | |
| Antiplatelet agents (*N*, %) | 3 (11.1%) | 2 (11.1%) | 1 (11.1%) | 1.000 |
| Anticoagulants (*N*, %) | 1 (3.7%) | 1 (5.6%) | 0 (0.0%) | 1.000 |
| Statins (*N*, %) | 3 (11.1%) | 2 (11.1%) | 1 (11.1%) | 1.000 |
| **Blood pressure on admission** | | | | |
| SBP (mm Hg)[b] | 160 (±27) | 162 (±30) | 156 (±23) | 0.608 |
| DBP (mm Hg)[b] | 95 (±19) | 96 (±20) | 92 (±16) | 0.635 |
| MBP (mm Hg)[b] | 117 (±20) | 118 (±22) | 113 (±17) | 0.608 |
| **Clinical scores on admission** | | | | |
| NIHSS[a] | 13.0 (5.0–36.0) | 13.5 (5.0–34.0) | 13.0 (3.0–36.5) | 0.897 |
| GCS[a] | 14.0 (6.0–15.0) | 14.0 (6.0–15.0) | 15.0 (4.5–15.0) | 0.956 |
| ICH score[a] | 1.0 (0.0–3.0) | 1.0 (0.0–3.0) | 1.0 (0.0–3.0) | 0.978 |
| **Laboratory indicators on admission** | | | | |
| Blood glucose (mmol/L)[b] | 12.2 (±5.3) | 11.8 (±5.4) | 13.1 (±5.4) | 0.453 |
| Hematocrit | 0.4 (±0.45) | 0.4 (±0.50) | 0.4 (±0.37) | 0.954 |
| INR[b] | 1.0 (±0.1) | 1.0 (±0.1) | 1.0 (±0.1) | 0.905 |
| Platelet ($10^9$/L)[b] | 176 (±56) | 167 (±56) | 193 (±56) | 0.271 |
| Serum creatinine (μmol/L)[b] | 96.6 (±44.6) | 105.1 (±52.2) | 80.0 (±13.8) | 0.161 |
| Length of stay (day)[a] | 13 (8–19) | 13 (7–18) | 13 (8–21) | 0.938 |

*CT, computed tomography; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean arterial pressure; NIHSS, National Institute of Health Stroke Scale; GCS, Glasgow Coma Score; ICH, intracerebral hemorrhage; INR, international normalized ratio.*

[a] *Median (quartile).*

[b] *Mean ± standard deviation.*

## DISCUSSION

The retrospective case-control study showed that pretreatment of sulfonylureas significantly associated with lower PHE and rPHE in diabetic patients who have acute basal ganglia hemorrhage. However, there was no significant difference on clinical outcomes between SFU and non-SFU patients at discharge.

Basal ganglia hemorrhage accounts for 50–70% of spontaneous intracerebral hemorrhage, and 35–44% of basal ganglia hemorrhage cases are due to hypertension (12, 13). In our study, we did not find any significant differences in patients with hypertension between the SFU and non-SFU groups. Regarding the use of sulfonylureas during hospitalization, significantly more patients in the SFU group received it than in the non-SFU group. Moreover, we found no difference in other treatments between the two groups.

Our findings provided evidence that an association existed between the pretreatment of sulfonylureas prior to the onset of ICH and decreased PHE and rPHE in the acute stage. This is in accordance with a previous clinical trial (7). Preclinical studies proved that sulfonylureas blocked the SUR1–TRPM4 channel from allowing ions to enter into cells. This resulted in reducing the formation of cytotoxic edema and vasogenic edema; then, sulfonylureas inhibited the secretion of the inflammatory mediator MMP-9 and eventually benefit ICH (14, 15). After adjusting for confounders, our results showed that the PHE volume and rPHE in SFU patients were smaller than those in non-SFU patients. In addition, in order to more accurately describe the effect of sulfonylureas on PHE, we used ICH volume as one of the matching factors instead of an outcome indicator.

For patients pretreated with sulfonylureas before admission, one previous study described improved discharge destination,

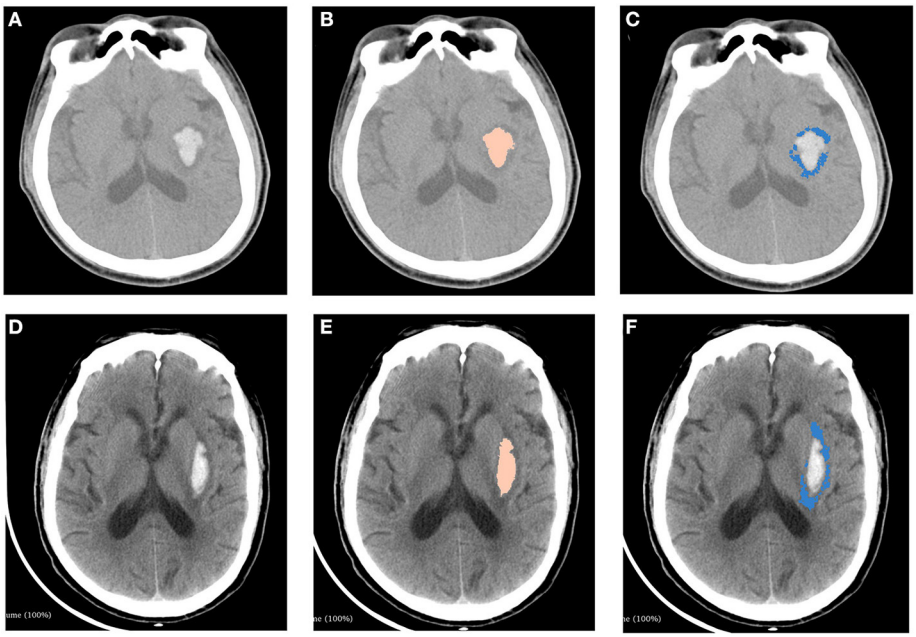


**FIGURE 2 |** Measurements of hematoma and perihematomal edema using 3D slicer software package. Two patients with similar ICH volumes but different PHE volumes were shown in this figure. Top panel: A patient with ICH from non-SFU group. **(A)** original image of head CT. **(B)** hematoma (5.0 ml) marked with pink. **(C)** PHE (6.7 ml) marked with blue. Bottom panel: A patient with ICH from SFU group. **(D)** original image of head CT. **(E)** hematoma(4.9ml) marked with pink. **(F)** PHE (4.2 ml) marked with blue. ICH, intracerebral hemorrhage; PHE, perihematomal edema.

**TABLE 2 |** Imaging characteristics on admission of sulfonylureas (SFU) and non-SFU patients.

| | Non-SFU patients (*N* = 18) | SFU patients (*N* = 9) | *P*-value |
|---|---|---|---|
| PHE volume (ml)[a] | 15.4 (7.4–50.2) | 8.0 (3.1–22.1) | 0.100 |
| rPHE[a] | 1.5 (1.2–1.9) | 0.8 (0.7–1.3) | 0.006 |
| Hematoma breaking into ventricles (*N*, %) | 6 (33.3%) | 2 (22.2%) | 0.676 |
| Midline shift (*N*, %) | 7 (38.9%) | 3 (33.3%) | 1.000 |

[a]*Median (quartile).*

**TABLE 3 |** Collinearity statistics of confounding factors in regression analysis.

| | PHE | | rPHE | |
|---|---|---|---|---|
| | Tolerance | VIF | Tolerance | VIF |
| Age | 0.654 | 1.530 | 0.654 | 1.530 |
| Gender | 0.536 | 1.864 | 0.536 | 1.864 |
| Time from onset to admission head CT | 0.676 | 1.480 | 0.676 | 1.480 |
| ICH volume | 0.276 | 3.619 | 0.276 | 3.619 |
| Hematoma breaking into ventricles | 0.626 | 1.598 | 0.626 | 1.598 |
| Midline shift | 0.213 | 4.701 | 0.213 | 4.701 |

*VIF, variance inflation factor.*
*The collinearity in regression analysis can be judged by two indicators: (1) when VIF ≥ 10, it indicates that there is serious multicollinearity between independent variables; and (2) when tolerance is <0.1, collinearity may be serious.*

**TABLE 4 |** Analysis of the associations between pretreatment of sulfonylureas use, perihematomal edema (PHE) volume and rPHE in sulfonylureas (SFU) and non-SFU patients.

| | Regression coefficient (95% CI) | *P-value* | Adjusted regression coefficient (95% CI) | Adjusted *P*-value |
|---|---|---|---|---|
| PHE volume | −17.816 (−36.874 to 1.243) | 0.066 | −13.607 (−26.185 to −1.029) | 0.035 |
| rPHE | −0.593 (−0.977 to −0.210) | 0.004 | −0.566 (−0.971 to −0.161) | 0.009 |

*Adjusted P-value by multiple linear regression analysis for confounders, including age, gender, time from onset to admission head CT, ICH volume, hematoma breaking into ventricles, and midline shift.*

and another study found that pretreatment with sulfonylureas was significantly associated with a lower likelihood of unfavorable functional outcome (mRS ≥ 3) at discharge (6, 7). Similar to a previous study (6), we used both mRS score and Barthel Index at discharge as parameters to assess the functional outcomes. However, pretreatment of sulfonylureas before the onset of ICH showed no significant improvement in clinical outcomes at discharge, even after we had adjusted for the confounding factors. One reason for the difference between our results and the two studies mentioned above may be that we limited the location of ICH to the basal ganglia; in those studies, the site of hematoma was not clearly defined. However, it was a determinant of functional outcomes (16).

Several potential limitations need to be taken into account. Firstly, our study was designed as a retrospective study with a

relatively small sample size; however, with our strict inclusion criteria as well as the 1:2 matching of cases and controls, it could represent the broader populations of ICH patients with diabetes. Secondly, due to the widespread use of different oral antidiabetic medications, the rate of sulfonylureas administration has largely decreased in Chinese diabetic patients, especially in the urban areas. For this reason, we studied all the sulfonylureas without limiting to a single drug. Thirdly, since it was difficult to obtain long-term follow-up data, the primary outcome of our study was based on imaging data rather than clinical outcomes. Lastly, we only analyzed admission CT scans because of a range of available antidiabetic agents during hospitalization. That might have different effects on outcomes, but it was what we had to do in real-world medical care. The limitations mentioned above must be recognized, but we believe that they would not invalidate the overall findings.

In conclusion, our study suggested that, for diabetic patients with acute basal ganglia hemorrhage, pretreatment of sulfonylureas may associate with lower PHE and relative PHE on admission. However, it has no significant effect on clinical outcomes at discharge. Future studies are needed to assess the potential clinical benefits in using sulfonylureas for ICH patients.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Xijing Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

This trial was conceived by YF and JW. ZhanJ and ZhaoJ collected the data, performed statistical analysis, and wrote the first version of the manuscript, with the advice from YF and JW. HB, WL, WJ, and WD assisted in data collection, statistical analysis, and manuscript modification. All authors are responsible for the designation and conduction of this study as well as the data analysis, the drafting, and the reviewing of the final content of the paper.

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# Stroke Lateralization in Large Hemisphere Infarctions: Characteristics, Stroke-Related Complications, and Outcomes

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**Objectives:** To assess the hemispheric differences in characteristics, stroke-related complications, and outcomes of patients with large hemisphere infarctions (LHI).

**Methods:** We enrolled consecutive patients admitted within 24 h after the diagnosis of LHI (defined as an ischemic stroke involving more than 50% of the territory of the middle cerebral artery in computed tomography and/or magnetic resonance imaging). Univariate and multivariate analysis were performed to explore the association between lateralization and stroke-related complications and clinical outcomes.

**Results:** A total of 314 patients with LHI were enrolled, with 171 (54.5%) having right hemispheric involvement. Right-sided patients with LHI had lower baseline National Institutes of Health Stroke Scale (NIHSS) score (18 vs. 22, $p < 0.001$), higher frequency of atrial fibrillation (69.0 vs. 52.4%, $p = 0.003$), and higher proportion of cardio-embolism (73.1 vs. 56.6%, $p = 0.013$) than the left. Right-sided LHI had higher incidence rates of malignant brain edema (MBE) (48.5 vs. 30.8%, $p = 0.001$) and a composite of cardiovascular events (29.8 vs. 17.5%, $p = 0.011$) during hospitalization. The incidence rate of 1-month mortality (34.5 vs. 23.8%, $p = 0.036$) was higher in right-sided patients with LHI, but there were no hemispheric differences in the incidence rates of 3-month mortality and unfavorable outcome (both $p > 0.05$). Multivariate analyses suggested right hemisphere involvement was independently associated with increased risk of MBE (adjusted OR 2.37, 95% CI 1.26–4.43, $p = 0.007$) and composite of cardiovascular events (adjusted OR 2.04, 95% CI 1.12–3.72, $p = 0.020$). However, it was not independently associated with 1-month death, 3-month mortality, and 3-month unfavorable outcome (all $p > 0.05$).

**Conclusions:** Right-sided patients with LHI had higher frequency of atrial fibrillation and cardio-embolism than the left-sided patients. Right hemisphere involvement was independently associated with increased risk of MBE and composite of cardiovascular events during hospitalization, whereas stroke lateralization was not an independent predictor of mortality and unfavorable outcome in patients with LHI.

**Keywords: hemispheric difference, complications, malignant brain edema, cardiovascular events, outcome, large hemispheric infarction**

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# INTRODUCTION

Large hemispheric infarction (LHI), which usually results from occlusion of the internal carotid artery or proximal middle cerebral artery (MCA), is a devastating condition with a high mortality rate (1, 2). LHI is commonly associated with varying degrees of brain swelling, with subsequently raised intracranial pressure, midline shift, and brain herniation, giving rise to the term malignant brain edema (MBE) (3). Until recently, no pharmacological strategies have been proven effective by clinical trials (4). Decompressive hemicraniectomy (DHC) conducted within 48 h after symptom onset has been proven effective for patients with LHI with MBE (5). However, only 0.3% of highly selected ischemic stroke patients would be eligible for DHC based on the strict eligibility criteria in the DHC trials (6).

It has also been reported that that poststroke complications are the leading cause of death and unfavorable outcomes in ischemic stroke patients (7, 8). Roth et al. have indicated that neurological impairment level is the most substantial factor predicting the rate of complications (9). Our previous work has demonstrated that stroke-related complication occurred in more than three fourths of the patients with LHI and was related to unfavorable outcome, whereas only MBE and pneumonia are independent predictors of a 3-month unfavorable outcome (10). As we know, the NIHSS score are weighted toward left hemisphere lesions (11). It is reasonable to suspect that stroke-related complications might frequently occur in left hemisphere stroke and result in poor outcomes. However, previous works have found that MBE seemed to be more common in the right hemisphere (12). Meanwhile, there is no consensus on the impact of the stroke hemisphere on outcomes of AIS (12–15).

Nowadays, limited data exist regarding the hemispheric differences in the incidence of stroke-related complications and outcomes of patients with imaging-diagnosed LHI. Therefore, we conducted a retrospective cohort study using the prospective data of Deyang stroke registry to assess the hemispheric differences in characteristics, stroke-related complications, and outcomes of patients with LHI.

# METHODS

## Study Design and Subjects

From January 1, 2016 to March 31, 2019, patients who were admitted to the Department of Neurology, People's Hospital of Deyang City with either a first-ever or recurrent acute ischemic stroke (AIS) were prospectively and consecutively registered. We enrolled patients who were admitted within 24 h from symptoms onset and diagnosed with LHI. LHI was defined as an infarction in the territory of the MCA, with computed tomography (CT) and/or magnetic resonance imaging (MRI) evidence of infarction that affected more than 50% of the territory of the MCA (with or without the involvement of other vascular territories) during hospitalization, and also an acute onset of corresponding clinical signs and symptoms (16). All patients had a non-contract CT (NCCT) scan before initial treatment. A routine follow-up NCCT or MRI scan was performed within the first 7 days of hospitalization. Other CT scans were performed in case neurological deterioration occurred to determine brain edema or hemorrhagic transformation. We excluded patients with bilateral hemisphere involvement. Cases with incomplete hospital records or missing imaging that would prevent complete data collection were excluded. We also excluded cases with a preexisting score of more than 2 on the modified Rankin scale (mRS) and who lived dependently (17).

The study protocol was approved by the Ethics Committee of People's Hospital of Deyang City (Reference No. 2011-04-134). Written informed consent was obtained from all patients before they were enrolled or from their legal representative if the patient lost the capacity to give informed consent.

## Data Collection and Outcome

Baseline data on age, sex, admission delay, initial stroke severity assessed by the National Institutes of Health Stroke Scale (NIHSS) score, baseline systolic and diastolic blood pressure, serum glucose on admission, and vascular risk factors were collected and compared according to the stroke side (left or right hemisphere involvement). The potential etiology of LHI was classified as cardio-embolism or not according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria (18). Two trained neurologists who were blinded to clinical information independently reviewed the imaging. A disagreement was resolved through discussion and consultation with a third neurologist. The presence of the HDMCAs was assessed on the pretreatment NCCT according to the following criteria (19): spontaneous visibility of the whole or part of horizontal segment of the MCA, the density of the MCA higher than that of the surrounding brain, disappearance on bone windows, unilaterality, and absence of subarachnoid bleeding. Early CT signs of hypodensity $>$ 1/3 MCA territory was defined as the substantial involvement of $\geq$2 of the following four areas: frontal, temporal, parietal, or both basal ganglia and insula (20). The ASPECTS was assessed on the pretreatment NCCT (21). Final infarct territory on the following-up imaging was dichotomized into MCA territory and MCA plus (involvement of other vascular territories besides the MCA territory). MBE was defined as the development of clinical signs of herniation (including decease in consciousness and/or anisocoria), accompanied by a midline shift of $\geq$5 mm at the septum pellucidum or pineal gland with effacement of the basal cisterns on follow-up imaging, without other known/apparent causes of deterioration (22). Hemorrhagic transformation during hospitalization was classified as hemorrhagic infarct (HI) and parenchymal hematoma (PH) based on follow-up CT or MRI according to the recommendations of the European Cooperative Acute Stroke Study (ECASS) criteria (23).

In-hospital treatments analyzed in our study included intravenous thrombolysis (IVT), endovascular interventions (EVT), DHC, mechanical ventilation, and osmotic agents (such as mannitol). IVT or EVT was performed according to the Chinese guidelines, and the inclusion and exclusion criteria were similar to those of the American guideline (24, 25). The final treatment decision was made in consultation with the neurologist and the patient's family. Post-EVT recanalization was evaluated on the digital subtraction angiography according to the Thrombolysis in Cerebral Infarction (TICI) grading system. Successful recanalization was defined as a TICI grade of

2b or 3 (26, 27). DHC was considered for patients with LHI with significant neurological deterioration and MBE, and the decision was finally made in consultation with neurosurgeons and the patient's family. Stroke-related complications, including both neurological and medical complications during hospitalization, were reviewed by data collectors who were not aware of the study from hospital records when the patient was discharged (10). Neurological complications included MBE, hemorrhagic transformation, post-stroke seizures/epilepsy, central hyperthermia, and recurrent stroke, whereas medical complications included composite of cardiovascular events, pneumonia, urinary tract infection, gastrointestinal bleeding, electrolyte disorder, acute renal failure, urinary incontinence, hypoalbuminemia, deep venous thrombosis, and bedsore, which have been elaborated in our previous study (10). Composite of cardiovascular events in our study was defined as a composite of myocardial infarction, or acute heart failure, or any sudden cardiac death (28).

Patients were followed-up at 90 days after stroke onset by using questionnaires *via* a telephone interview or by mail. The primary outcome measures in our study were 1-month mortality, 3-month mortality, and unfavorable outcome [defined as an mRS score of 4 to 6 (17)].

## Statistical Analyses

The primary objective of our work was to test whether hemispheric side of LHI influenced the incidence of stroke-related complications and clinical outcomes. Baseline characteristics, in-hospital treatment, stroke-related complications, and outcomes were compared between patients with LHI with left-side and right-side lesions. Intergroup differences in categorical variables were assessed for significance using the $\chi^2$ tests or Fisher's exact tests, whereas differences in continuous variables were assessed using Student's *t*-tests or the Mann-Whitney *U*-test. Univariate analysis was performed to test variables that might affect the occurrence of stroke-related complications and outcomes. The included variables were: (1) age, (2) baseline NIHSS score, (3) vascular risk factors surveyed in our study, (4) imaging characteristics, (5) in-hospital treatment. The 3-month survival was estimated by the Kaplan–Meier method and a log-rank test was used for survival comparisons between patient groups. Multivariate analyses were performed to identify the association between the lateralization and the occurrence of stroke-related complications and outcomes, *via* adjusting for potential confounders (variables with $p < 0.1$ in univariate analyses). The 95% CI were calculated to describe the precision of the estimates. All statistical analysis was performed using SPSS v21.0 (SPSS, Chicago, IL). Two-sided $p < 0.05$ was considered to be statistically significant.

# RESULTS

During the study period, 3,551 patients with AIS were registered. Of those patients, 314 (8.8%) unilateral patients with LHI admitted with 24 h were enrolled in the present study [mean age: 68.1 ± 14.8 years; 181 (57.6%) men; median NIHSS score on

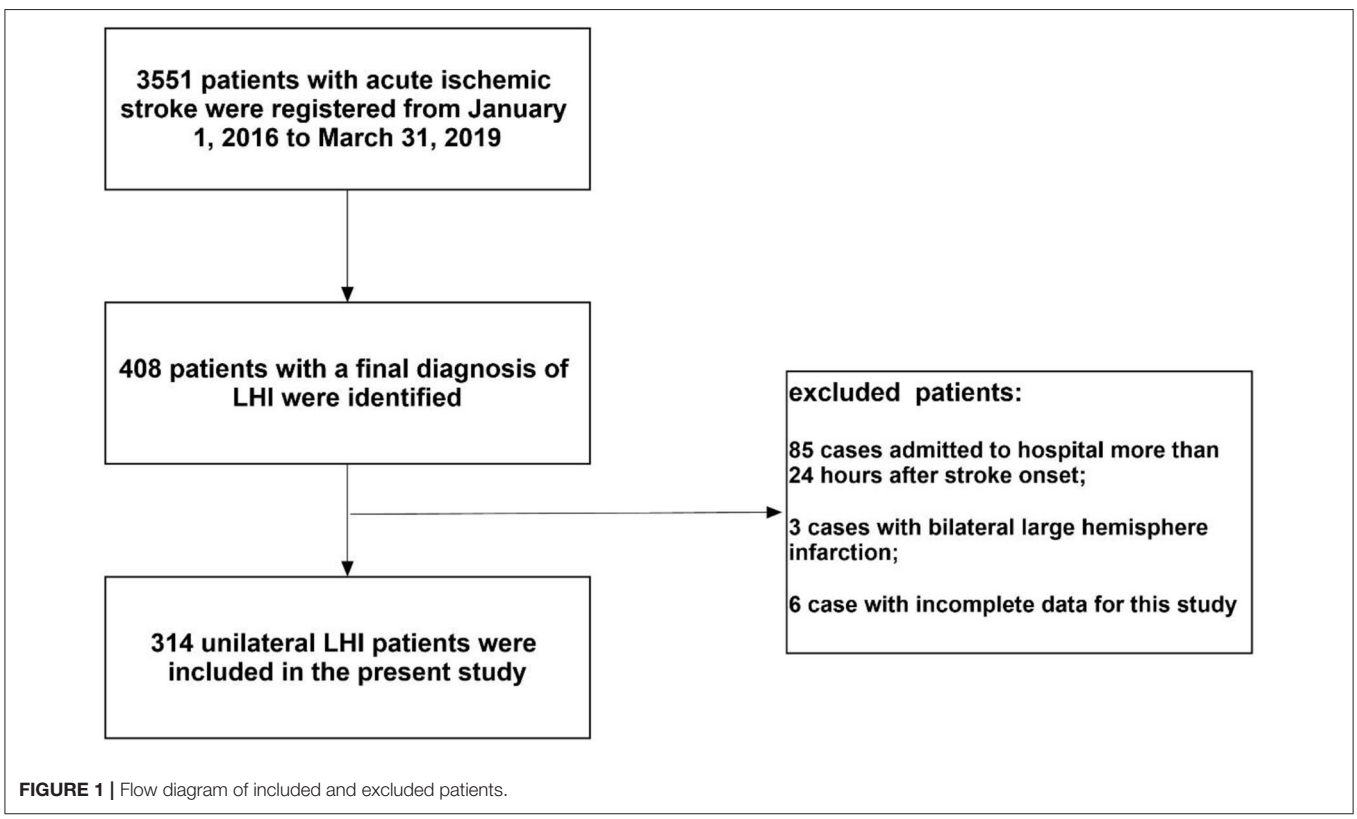


**FIGURE 1 |** Flow diagram of included and excluded patients.

admission: 20]. A flow diagram of included and excluded patients is provided in **Figure 1**. All patients with LHI received CT scan at least one time and 156 (49.7%) patients received MRI. Among the enrolled patients, 171 (54.5%) were right hemisphere stroke and 143 (45.5%) were left hemisphere stroke. Sixty-one (19.4%) cases were treated with IVT and 46 (14.6%) were treated with EVT at the hyperacute stage. Thirty (9.6%) cases received DHC and 99 (31.5%) received mechanical ventilation during hospitalization. Five (1.6%) cases were lost to follow-up and 93 (29.6%) patients died at 30 days. Seven (2.2%) patients were lost to follow-up at 90 days (three in right-sided group and four in left-sided group). Among the entire cohort, 104 (33.1%) patients died and 221 (70.4%) patients had unfavorable outcome at 3 months.

## Hemispheric Differences in Characteristics and In-hospital Treatment

Compared with left hemisphere stroke, patients with LHI with right-side lesions had lower baseline NIHSS score (18 vs. 22, $p < 0.001$). Right hemisphere LHI showed higher rate of atrial fibrillation (69.0 vs. 52.4%, $p = 0.003$) and higher proportion of cardio-embolism (73.1 vs. 56.6%, $p = 0.013$) than the left. There was no difference in the mean age, gender, median admission delay, baseline blood pressure, baseline serum glucose, or other vascular risk factors between the two groups (all $p > 0.05$). Right hemispheric LHI had a lower median ASPECTS (six vs. seven, $p = 0.004$) and a higher rate of basal ganglia involvement on the pretreatment NCCT (70.2 vs. 58.0%, $p = 0.025$); however, the presence of HDMCAS, hypodensity > 1/3 of the MCA territory on baseline CT scan, and final infarct territory were comparable between the two groups (all $p > 0.05$). Then 21 (12.3%) cases with right hemisphere involvement and 25 (17.5%) cases with left hemisphere involvement were treated with EVT ($p = 0.194$) at the hyperacute stage. Among those patients, successful recanalization was achieved in 12 (57.1%) right-sided LHI patients and 20 (80.0%) left-sided patients. Patients with LHI with right-side involvement more frequently received DHC (14.0 vs. 4.2%, $p = 0.003$). There was no difference in the administration rate of IVT, mechanical ventilation, and osmotic therapy (all $p > 0.05$) (**Table 1**).

**TABLE 1 |** Hemispheric differences in baseline characteristics and in-hospital treatment of LHI patients.

| | Right hemisphere ($n = 171$) | Left hemisphere ($n = 143$) | *P*-value |
|---|---|---|---|
| Age (years), mean ± SD | 69.1 ± 14.2 | 66.9 ± 15.5 | 0.180* |
| Male, *n* (%) | 91 (53.2) | 90 (62.9) | 0.083‡ |
| Time from onset (h), median (range) | 5 (3-11) | 5 (3-14) | 0.771† |
| Baseline NIHSS score, median (range) | 18 (15-22) | 22 (20-25) | **<0.001**† |
| SBP on admission (mm Hg) | 140.3 ± 24.5 | 143.1 ± 25.1 | 0.326* |
| DBP on admission (mm Hg) | 83.0 ± 16.2 | 82.2 ± 13.9 | 0.659* |
| Baseline serum glucose (mmol/L) | 8.2 ± 2.4 | 7.8 ± 2.8 | 0.259* |
| **Risk factors, *n* (%)** | | | |
| Hypertension | 94 (55.0) | 67 (46.9) | 0.152‡ |
| Diabetes mellitus | 39 (22.8) | 29 (20.3) | 0.588‡ |
| Dyslipidemia | 36 (21.1) | 30 (21.0) | 0.987‡ |
| Coronary heart disease | 29 (17.0) | 16 (11.2) | 0.146‡ |
| Atrial fibrillation | 118 (69.0) | 75 (52.4) | **0.003**‡ |
| Rheumatic heart disease | 25 (14.6) | 19 (13.3) | 0.735‡ |
| Current smoking | 54 (31.6) | 52 (36.4) | 0.372‡ |
| Alcohol consumption | 43 (25.1) | 33 (23.1) | 0.670‡ |
| Previous ischemic stroke/TIA | 27 (15.8) | 21 (14.7) | 0.787‡ |
| Previous ICH | 2 (1.2) | 2 (1.4) | 0.857‡ |
| TOAST classification, *n* (%) | | | **0.013**‡ |
| Large-artery atherosclerosis | 20 (11.7) | 25 (17.5) | |
| Cardio-embolism | 125 (73.1) | 81 (56.6) | |
| Other determined etiology | 5 (2.9) | 12 (8.4) | |
| Undetermined etiology | 21 (12.3) | 25 (17.5) | |
| HDMCAS, *n* (%) | 51 (29.8) | 34 (23.8) | 0.230‡ |
| Hypodensity > 1/3 MCA territory | 51 (29.8) | 33 (23.1) | 0.191‡ |
| ASPECTS, median (range) | 6 (4-8) | 7 (5-9) | **0.004**† |
| Basal ganglia Involvement | 120 (70.2) | 83 (58.0) | **0.025**‡ |
| Final infarct territory | | | 0.066‡ |
| MCA | 142 (83.0) | 129 (90.2) | |
| MCA plus | 29 (17.0) | 14 (9.8) | |
| **Treatments, *n* (%)** | | | |
| Intravenous thrombolysis^ | 34 (19.9) | 27 (18.9) | 0.823 |
| Endovascular interventions^ | 21 (12.3) | 25 (17.5) | 0.194 |
| DHC^ | 24 (14.0) | 6 (4.2) | **0.003** |
| Mechanical ventilation^ | 61 (35.7) | 38 (26.6) | 0.084 |
| Osmotic agents^ | 166 (97.1) | 134 (93.7) | 0.150 |

*SD, Standardized difference; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; TOAST, Trial of Org 10172 in Acute Stroke Treatment; TIA, transient ischemic stroke; ICH, intracerebral hemorrhage; HDMCAS, hyperdensity in the middle cerebral artery (MCA); DHC, decompressive hemicraniectomy.*

**Student t-test. †Mann–Whitney U-test. ‡$\chi 2$ test. The bold values indicates $p < 0.05$. ^Acute phase treatment.*

## Hemispheric Differences in the Incidence of Stroke-Related Complications

Large hemisphere infarctions patients with right hemisphere involvement had higher incidence rates of MBE (48.5 vs. 30.8%, $p = 0.001$) and composite of cardiovascular events (29.8 vs. 17.5%, $p = 0.011$) during hospitalization than those with left-side lesions (**Figure 2**). However, no significant difference was found in the incidence rate of total hemorrhagic transformation (48.0 vs. 49.0%, $p = 0.860$), HI (18.1 vs. 18.9%, $p = 0.864$), and PH (29.8 vs. 30.1%, $p = 0.962$) between right and left hemisphere stroke patients. Meanwhile, there was no significant difference in the events rates of seizures/epilepsy, central hyperthermia, recurrent stroke, pneumonia, urinary tract infection, gastrointestinal bleeding, electrolyte disorder, acute renal failure, urinary incontinence, hypoalbuminemia, deep venous thrombosis, and bedsore between right and left hemisphere stroke patients (all $p > 0.05$) (**Table 2**). After adjusting for age, baseline NIHSS score and other confounders in multivariate analyses, right hemisphere involvement was independently associated with increased risk of MBE (adjusted

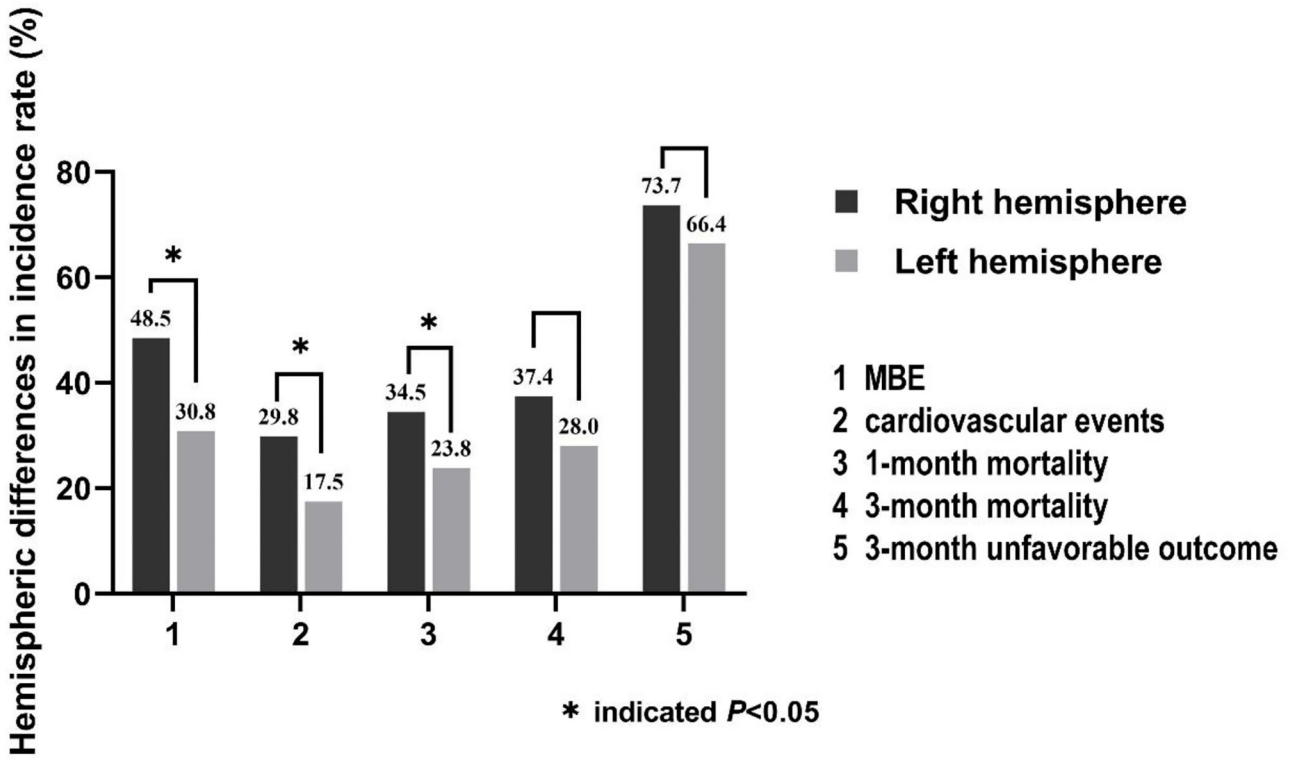


**FIGURE 2 |** Hemispheric differences in the incidence rates of stroke-related complications (MBE and composite of cardiovascular events) and clinical outcomes.

OR 2.37, 95% CI 1.26–4.43, $p = 0.007$) and composite of cardiovascular events (adjusted OR 2.04, 95% CI 1.12–3.72, $p = 0.020$) (**Table 3**).

Since the occurrence of MBE is closely related to whether EVT was carried out, the recanalization status (successful recanalization or not), and also whether there was hemorrhagic transformation, we conducted a sensitivity analysis including EVT, successful recanalization, and hemorrhagic transformation in the multivariate analysis. After adjusting for confounders, right-sided stroke was still an independent factor associated with increased risk of MBE in LHI patients (adjusted OR 3.12, 95% CI 1.55–6.29, $p = 0.001$).

## Hemispheric Differences in the Outcomes

The incidence rate of 1-month mortality (34.5 vs. 23.8%, $p = 0.036$) was higher among LHI patients with right hemisphere involvement, but there were no hemispheric differences in the incidence rates of 3-month mortality (37.4 vs. 28.0%, $p = 0.086$) and 3-month unfavorable outcome (73.7 vs. 66.4%, $p = 0.196$) (**Figure 2**; **Table 2**). Meanwhile, the 3-month survival rate of the right hemispheric LHI estimated by Kaplan-Meier Method was not significantly higher than the left-sided ($p = 0.071$, log-rank test; **Figure 3**). After adjusting for age, baseline NIHSS score, baseline systolic blood pressure, baseline serum glucose, hypodensity > 1/3 MCA territory on baseline CT scan, ASPECTS, involvement of other vascular territories besides the MCA territory, EVT, DHC, and mechanical ventilation, which had a potential association with death and unfavorable outcomes of LHI patients in univariate analysis, right hemisphere involvement was not independently associated with 1-month mortality, 3-month mortality, and 3-month unfavorable outcome of LHI patients (all $p > 0.05$, see in **Table 3**).

# DISCUSSION

Several studies have reported the left-right propensity of cardioembolic infarcts, but no consensus has been reached so far (29–34). Although the left hemisphere propensity of cardiogenic emboli has been reported (29, 30), some researches supported the right-sided propensity of cardio-embolism, especially those associated with atrial fibrillation (31, 32). A recently published work indicated that bovine aortic arch was associated with left hemisphere laterality of cardioembolic stroke compared with standard arches (33). Another work suggested that there was a trend toward right-sided lesions in patients with standard arches, but no significant difference in cardio-embolic stroke laterality of patients with bovine arches was demonstrated (34). In this work, we found that LHI patients with right hemisphere involvement had higher frequency of atrial fibrillation and cardio-embolism, supporting the right-sided propensity of cardio-embolism in LHI patients. It is worth noting that although there were 1.6% (5/314) left-handed patients (all with right hemisphere infarction) in the present cohort, there was no significant difference in the presence of left-handedness among LHI patients with a stroke etiology

**TABLE 2 |** Hemispheric differences of and stroke-related complications during hospitalization in LHI patients.

| | Right hemisphere ($n$ = 171) | Left hemisphere ($n$ = 143) | $P$-value |
|---|---|---|---|
| **Neurological complications, *n* (%)** | | | |
| Malignant brain edema | 83 (48.5) | 44 (30.8) | **0.001** |
| Hemorrhagic transformation | 82 (48.0) | 70 (49.0) | 0.860 |
| HI | 31 (18.1) | 27 (18.9) | 0.864 |
| PH | 51 (29.8) | 43 (30.1) | 0.962 |
| Seizures/epilepsy | 11 (6.4) | 13 (9.1) | 0.377 |
| Central hyperthermia | 23 (13.5) | 10 (7.0) | 0.063 |
| Recurrent stroke | 4 (2.3) | 1 (0.7) | 0.381* |
| **Medical complications, *n* (%)** | | | |
| Composite of cardiovascular events | 51(29.8) | 25(17.5) | **0.011** |
| Pulmonary infection | 129 (75.4) | 109 (76.2) | 0.871 |
| Urinary tract infection | 36 (21.1) | 30 (21.0) | 0.987 |
| Gastrointestinal bleeding | 71 (41.5) | 62 (43.4) | 0.743 |
| Electrolyte disturbance | 105 (61.4) | 80 (55.9) | 0.327 |
| Acute renal failure | 43 (25.1) | 27 (18.9) | 0.184 |
| Hypoalbuminemia | 84 (49.1) | 70 (49.0) | 0.976 |
| Urinary incontinence | 35 (20.5) | 28 (19.6) | 0.845 |
| Deep venous thrombosis | 16 (9.4) | 15 (10.5) | 0.738 |
| Bedsore | 4 (2.3) | 3 (2.1) | 1.000* |
| **Clinical outcomes, *n* (%)** | | | |
| 1-month mortality | 59 (34.5) | 34 (23.8) | **0.036** |
| 3-month mortality | 64 (37.4) | 40 (28.0) | 0.086 |
| 3-month unfavorable outcome | 126 (73.7) | 95 (66.4) | 0.196 |

**Fisher's exact test. The bold values indicates p < 0.05.*

**TABLE 3 |** Univariate and multivariate analyses for the association between right hemisphere involvement and stroke-related complications and outcome in LHI patients.

| | Univariate analysis | | Multivariate analysis* | |
|---|---|---|---|---|
| | OR (95%CI) | $P$-value | OR (95%CI) | $P$-value |
| Malignant brain edema | 2.12 (1.33-3.38) | **0.002** | 2.37 (1.26-4.43)[a] | **0.007** |
| Composite of cardiovascular events | 2.01 (1.17-3.45) | **0.012** | 2.04 (1.12-3.72)[b] | **0.020** |
| 1-month mortality | 1.70 (1.03-2.81) | **0.037** | 1.42 (0.73-2.73)[c] | 0.302 |
| 3-month mortality | 1.52 (0.94-2.47) | 0.087 | 1.21 (0.62-2.34)[c] | 0.574 |
| 3-month unfavorable outcome | 1.39 (0.84-2.29) | 0.197 | 1.20 (0.59-2.45)[d] | 0.616 |

**Adjusted for variables which had a significant association with corresponding stroke-related complications and clinical outcomes in univariate analysis.*
*OR, odds ratios; CI,confidence intervals.*
*[a]Adjusted for age, baseline NIHSS score, baseline diastolic blood pressure, TOAST classification, hypodensity > 1/3 MCA territory on baseline CT scan, baseline ASPECTS, basal ganglia involvement, involvement of other vascular territories besides the MCA territory, and EVT, which had a potential association with malignant brain edema in univariate analysis.*
*[b]Adjusted for age, sex, baseline NIHSS score, predisposing vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, previous ischemic stroke/TIA, current smoking and alcohol consumption), prior-to-stroke heart diseases (coronary heart disease, atrial fibrillation, rheumatic heart disease), and acute reperfusion therapies (IVT and EVT), which had a potential association with composite of cardiovascular events in univariate analysis.*
*[c]Adjusted for age, baseline NIHSS score, baseline systolic blood pressure, baseline serum glucose, hypodensity > 1/3 MCA territory on baseline CT scan, ASPECTS, involvement of other vascular territories besides the MCA territory, EVT, DHC and mechanical ventilation, which had a potential association with death of LHI patients in univariate analysis.*
*[d]Adjusted for age, baseline NIHSS score, baseline systolic blood pressure, baseline serum glucose, hypodensity > 1/3 MCA territory on baseline CT scan, ASPECTS, involvement of other vascular territories besides the MCA territory, EVT, DHC and mechanical ventilation, which had a potential association with death of LHI patients in univariate analysis. The bold values indicates p < 0.05.*

of cardiogenic embolism or not, supporting that the right-sided propensity of cardio-embolism in LHI patients was independent of whether it was a non-dominant hemisphere or not. Our results could be explained by the fact that the brachiocephalic artery is the first branch off the aortic arch, has the largest ostium, and heads upward and parallel to the direction of the ascending aorta. So large-sized cardiogenic emboli would therefore have a higher propensity to enter the brachiocephalic artery (which supplies the right common carotid and right subclavian) rather than the left common carotid artery, which arises second from the aortic arch and has an orientation perpendicular to it (33–35). Further study is warranted to determine whether there is a difference in the laterality of cardiogenic infarct depending on the size of embolic particles besides the aortic arch branching pattern.

Previous works have suggested that higher baseline NIHSS score was one of the early predictors for MBE after ischemic stroke (36). Meanwhile, the NIHSS score are also weighted toward left hemisphere lesions (11). As a result, right hemisphere infarctions can be deemed to be less severe than left-sided, such that physicians and surgeons might be less aggressive in treatment. However, our study found that patients with LHI with right hemisphere involvement had higher incidence rate of MBE (48.5 vs. 30.8%) than those with the left. Multivariate analysis suggested that right hemisphere stroke (OR 2.37, 95 % CI 1.26-4.43) was an independent risk factor of MBE in patients with LHI. Although there was a lower successful recanalization rate of right-sided stroke patients following EVT in our cohort (57.1 vs. 80.0%), multivariate analysis including EVT, successful recanalization, and hemorrhagic transformation also identified right hemisphere involvement as an independent risk factor of MBE in LHI patients. These results are consistent with the result of a systematic review, which included a total of 73 relevant studies and concluded that "malignant" MCA infarction appears to be more common in the right hemisphere (12). These results can be explained because the right hemisphere plays a crucial role in cardiovascular regulation due to autonomic nervous system lateralization, leading to greater alterations of norepinephrine levels and sympathetic activation after right hemispheric insular infarction than the left (37). Increased levels of norepinephrine can result in vasoconstriction, increasing the permeability of blood–brain barrier and the levels of extracellular glutamate by stimulation of β-adrenoreceptor, creating an intracellular $Ca^{2+}$ and $Na^{+}$ osmotic gradient and thus attracting extracellular fluid into the cell resulting in the development of cytotoxic edema (12, 37, 38). Moreover, increased levels of norepinephrine can stimulate the α-1 adrenergic receptors in the supraoptic nucleus of the hypothalamus and thereby enhance the release

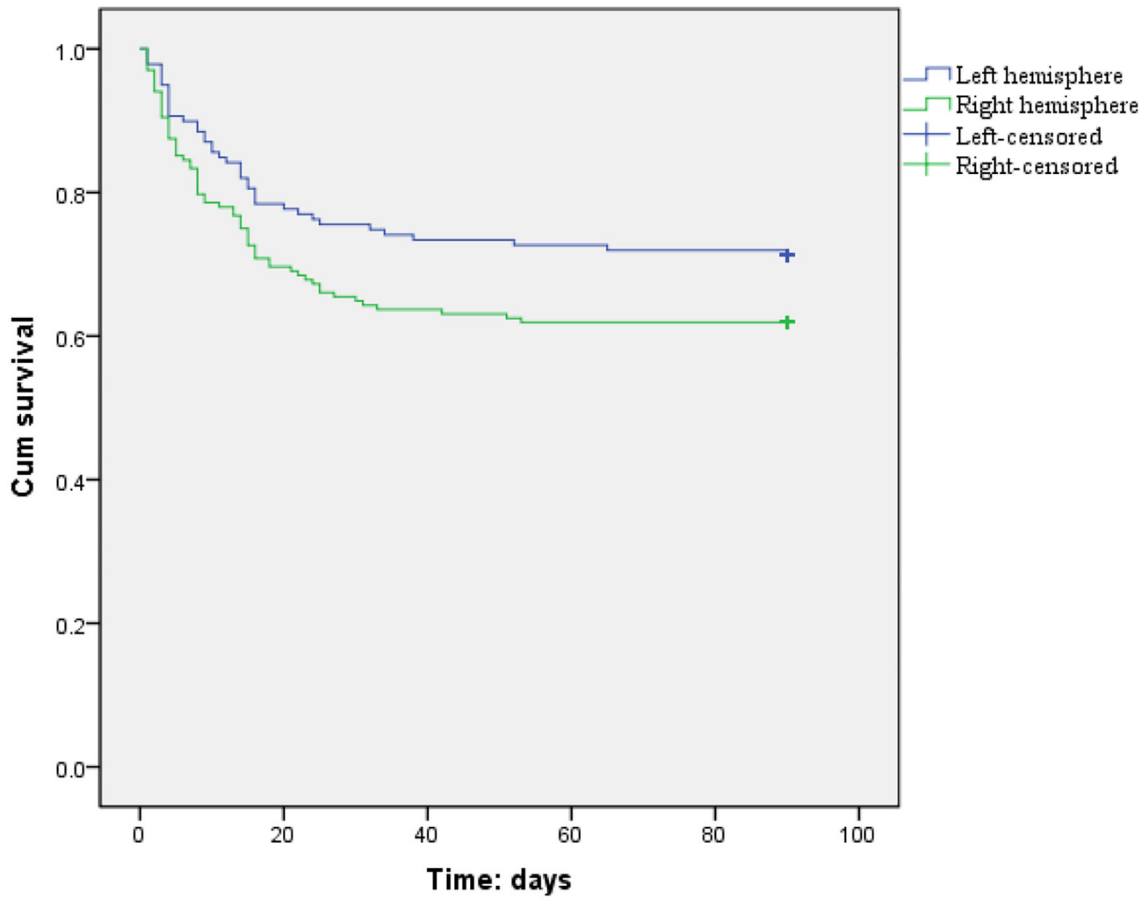


**FIGURE 3 |** Three-month survival curves for LHI patients estimated by Kaplan–Meier analysis (patients with right or left hemisphere involvement, $p = 0.071$, log rank test).

of vasopressin, leading to the downregulation of aquaporin-4 and increasing the plasma membrane permeability (12, 39). Vasopressin can also participate in the ischemic cascade, leading to neuroinflammation, necrosis, and apoptosis that might be another factor in the asymmetrical development of MBE (12, 39).

Several clinical works indicate that the effect on the cardiovascular system depends on the stroke lateralization (40–43). It has been reported that when brain damage affects the right insular cortex, the consequences on cardiac function are more deleterious and more frequent (40–42). Conversely, another work indicates that left insular stroke appears to be an independent predictor of severe cardiovascular consequences such as cardiac death, acute myocardial infarction, angina, or heart failure (41). The phenomenon of stroke lateralization has also been observed in experimental models (44, 45). It has been demonstrated that right MCA occlusion (MCAO) in rats had more cardiovascular consequences than the left MCAO (44, 45). In our work, we found that right-sided LHI patients had higher rate of composite of cardiovascular events (29.8 vs. 17.5%) during hospitalization than the left-sided. After adjusting for age, sex, baseline NIHSS score, predisposing vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, previous ischemic stroke/TIA, current smoking, and alcohol consumption), prior-to-stroke heart diseases (coronary heart disease, atrial fibrillation, rheumatic heart disease), and acute reperfusion therapies (IVT and EVT), which had a potential association with composite of cardiovascular events, right hemisphere involvement was still an independent risk factor of composite of cardiovascular events in patients with LHI (OR 2.04, 95% CI 1.12–3.72). This result could be explained by the fact that right hemisphere stroke, especially those with insular cortex involvement, is responsible for autonomic disturbances and triggers inflammatory processes including the release of cytokines such as monocyte chemoattractant protein-1, C-reactive protein, growth differentiation factor, leading to an increased risk of cardiac death, acute myocardial infarction, and heart failure (46).

Our work found that although the right-sided LHI had higher incidence rate of 1-month mortality (34.5 vs. 23.8%) in univariate analysis, multivariate analysis suggested that stroke lateralization was not an independent predictor of mortality and unfavorable outcome in LHI patients. Previous studies have not reached a consensus on the impact of the stroke hemisphere on outcomes of AIS (12–15). A cohort study indicated that left-hemispheric AIS were often associated with a worse outcome than their right-hemispheric counterparts (14). However, several studies

suggested an association between right hemisphere involvement and higher risk of death and unfavorable functional outcome in AIS patients, especially for those with mild/moderate strokes (13, 47). The results of our work are in line with previous published systematic review and metaanalysis, which indicated that stroke lateralization was not an independent predictor of mortality and unfavorable outcome and did not modify the treatment effect of MCA territorial infarction (12, 15).

### Limitations

The results of the present work should be interpreted with caution given its limitations. First, we conducted a retrospective study using the prospective data from the Deyang stroke registry, and so we could not provide information related to inflammatory cytokines and markers of myocardial injury such as C-reactive protein, troponins, or other acute-phase protein, and further studies are needed to explore this issue. Second, it was a single hospital-based study, with limited generalizability. Some patients with severe LHI might not be hospitalized, especially those who died before being admitted to the hospital, and so we could not exclude inclusion bias in this study. Third, follow-up in our study was performed by telephone interview or a mailed questionnaire instead of a clinic visit which may result in reporting bias.

## CONCLUSIONS

We identified that patients with LHI with right hemisphere involvement had higher frequency of atrial fibrillation and cardio-embolism. Right hemisphere involvement was independently associated with increased risk of MBE and composite of cardiovascular events during hospitalization, whereas hemispheric difference was not an independent predictor of mortality and unfavorable outcome in LHI patients. Implement of early pharmacological or non-pharmacological intervention for autonomic restoration might improve the outcome of right-sided LHI patients, especially those with insular cortex involvement.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the corresponding author on reasonable request.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of People's Hospital of Deyang City. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

JL and PZ collected, analyzed, and interpreted the data, as well as drafted the manuscript. YL and WC participated in data interpretation and revised the manuscript. XY participated in study conception and design. CW contributed substantially to study design and supervision, data interpretation and manuscript writing. All authors critically revised the manuscript for important intellectual content and approved the final manuscript.

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BRIEF RESEARCH REPORT
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# The Benefit of Thrombectomy in Patients With Low ASPECTS Is a Matter of Shades of Gray—What Current Trials May Have Missed

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Randomized trials supporting the benefit of endovascular treatment in acute ischemic stroke patients with a large early infarction are not yet available. Few retrospective studies exist that suggest a potential positive treatment effect on functional outcome, as well as procedural safety. However, potential benefit or harm of MT in patients with low initial ASPECTS is still a subject of current debate, and in particular, how to select these patients for treatment. The purpose of this pilot study was to evaluate how early tissue water uptake in acute ischemic brain might determine lesion fate and functional outcome in low ASPECTS patients undergoing MT. We observed that the degree of early water uptake measured by quantitative NWU was significantly associated with functional outcome in low ASPECTS patients, yielding a higher diagnostic power compared to other parameters such as ASPECTS, age, or NIHSS. No conclusive evidence of a beneficial effect of successful reperfusion was observed in patients with low ASPECTS and high NWU, which highlights the potential of NWU as a tool to specify patient selection.

**Keywords: stroke, edema, thrombectomy, infarct, outcome**

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## RANDOMIZED TRIALS OF THROMBECTOMY IN PATIENTS WITH LARGE EARLY INFARCTS

Randomized clinical trial data supporting the benefit of endovascular treatment in acute ischemic stroke patients with a large early infarction are not yet available (1). Few retrospective studies exist that suggest a potential positive treatment effect on the functional outcome, as well as procedural safety (2–7). However, the potential benefit or harm of MT in patients with low inital ASPECTS is still a subject of current debate, and, in particular, how to select these patients for treatment. There is uncertainty of how to operationalize a threshold of extensive early infarct in CT to safely guide MT, which is reflected by the different inclusion criteria of the current low ASPECTS trials. TENSION and SELECT-2 include patients with ASPECTS 3–5, while LASTE (InExtremis) and TESLA include patients with 0–5 and 2–5, respectively (3–5 in LASTE for patients with > 80 years old) (8). Moreover, trials differ regarding the time window from the symptom onset to imaging, NIHSS cut-offs, or neuroimaging modality. The utilization of perfusion CT (CTP) as a selection tool has recently been critized with regard to overestimation of the true volume of irreversibly injured brain tissue, especially in the early time window, and in the context of the SELECT-2 trial

(9–13). In particular, the exclusion of large core patients but ASPECTS >5 and/or early time window is controversial (9).

The rating of ASPECTS itself is based on binary scoring for presence of hypoattenuated brain tissue in 10 predefined territorial areas of the middle cerebral artery. This tissue hypoattenuation is directly related to early infarct with edematous water uptake, which can be quantified on CT (14). However, ASPECTS does not differentiate between different degrees of hypoattenuation in binary scored regions. Hence, the level of hypoattenuation (i.e., the level of water uptake indicated ischemic progression) may significantly differ across identical low ASPECTS ratings even after a similar time from the onset to imaging. It is thus conceivable that the potential benefit of MT in patients with low ASPECTS heavily depends on ischemic progression indicated by water uptake .

The purpose of this pilot study was to evaluate how early tissue water uptake in acute ischemic brain might determine lesion fate and the functional outcome in patients with low ASPECTS undergoing MT. We hypothesized that quantitative lesion water uptake measured in admission-CT differentiates patients with low ASPECTS with respect to the functional outcome after MT and predicts futile vessel recanalization.

# PILOT STUDY—EARLY TISSUE WATER UPTAKE AS A DETERMINANT OF RESPONSE TO MT

## Improving Low ASPECTS Stroke Thrombectomy (I-LAST)

I-LAST is an academic, independent, prospective, multicenter, observational registry study. This study aims to investigate the role of advanced imaging biomarkers in patients with large early infarct. The study is in accordance with the ethical guidelines of the local ethics committee and with the Declaration of Helsinki. The local ethics committee approved this study (WF-091/21) and waived informed consent. The study is registered within the ClinicalTrials.gov Protocol Registration and Results System (NCT04862507). The present pilot study used similar inclusion criteria (as stated below) and serves as an exploratory analysis to investigate the potential value of lesion water uptake as an imaging biomarker in the triage of patients with low ASPECTS.

## Patient Inclusion

For this exploratory pilot study, anonymized data from a tertiary-care stroke center were analyzed retrospectively.

All patients with acute ischemic stroke due to a large vessel occlusion in the anterior circulation admitted between March 2017 and March 2019 were consecutively screened for patients with (1) CT-angiography-confirmed occlusion of the M1 segment of the middle cerebral artery (MCA) or distal occlusion of the internal carotid artery (ICA); (2) admission multimodal CT protocol with non-enhanced CT (NECT), CT-Angiography (CTA), and Perfusion-CT (CTP) performed within 12 h from the symptom onset; (3) An initial ASPECTS of 5 or less in admission-NECT rated by a board-certified neuroradiologist. Decision for treatment was made by a board-certified neurointerventionalist in consensus with a board-certified attending stroke neurologist. Ischemic lesion net water uptake (NWU) was quantified as previously described (15, 16). A region of interest (ROI) was placed for density measurements according to the extent of ischemic hypoattenuation identified on NECT with hindsight knowledge of the core lesion in cerebral blood volume (CBV).

All finally analyzed patients were included in the regression analyses. Successful recanalization was defined as modified thrombolysis in cerebral infarctions (mTICI) score 2b-3. The patients who did not undergo MT were defined to have "no successful vessel recanalization."

We compared the medians of the independent variables using Mann-Whitney U tests for patients based on the functional outcome at Day 90 after dichotomization in "good" (mRS 0–2) and "poor" outcomes (mRS 3–6). Receiver operating characteristic (ROC) curve analyses were performed to assess the area under the curve (AUC) of the independent variables [ASPECTS, NWU (continuous), age, and NIHSS] to compare its diagnostic ability to discriminate the functional outcome (dependent variable: mRS 0–2). Furthermore, a multivariable logistic regression analysis was performed using ASPECTS, NWU (continuous), age, time from the onset to imaging, NIHSS, and recanalization status as independent variables with stepwise variable selection. Moreover, "MT" was tested as an independent variable replacing "recanalization status." The intention was to assess the independent association of NWU and the functional outcome, adjusted for covariates, especially ASPECTS, and recanalization status. We also tested the association of recanalization and the outcome separately for the patients with low and high NWU, distinguished using the NWU cut-off from ROC analysis. Finally, multivariable logistic regression analysis was performed with mRS 0–3 as a dependent variable, as the number of patients with functional independence (mRS 0–2) at Day 90 may be limited due to more distinctive baseline infarction.

A statistically significant difference was accepted at a $p$-value of $< 0.05$. Analyses were performed using MedCalc (version 11.5.1.0; Mariakerke, Belgium) and R (R Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Vienna, Austria, 2017).

## Ethics Statement

Anonymized data were recorded and analyzed in accordance with ethical guidelines and after approval of the local ethics committee. Informed consent was waived.

# RESULTS

About 155 patients were analyzed. The median ASPECTS was 4 (IQR: 3–5), and the mean NWU at admission was 10.8% (SD: 3.8%). The median age was 75 (IQR: 66–82). Seventy-eight patients (50.3%) underwent MT, of which 50 (64%) resulted in successful endovascular recanalization (mTICI $\geq$ 2b). The median mRS at Day 90 was 5 (IQR: 4–6) with 17 (11%)

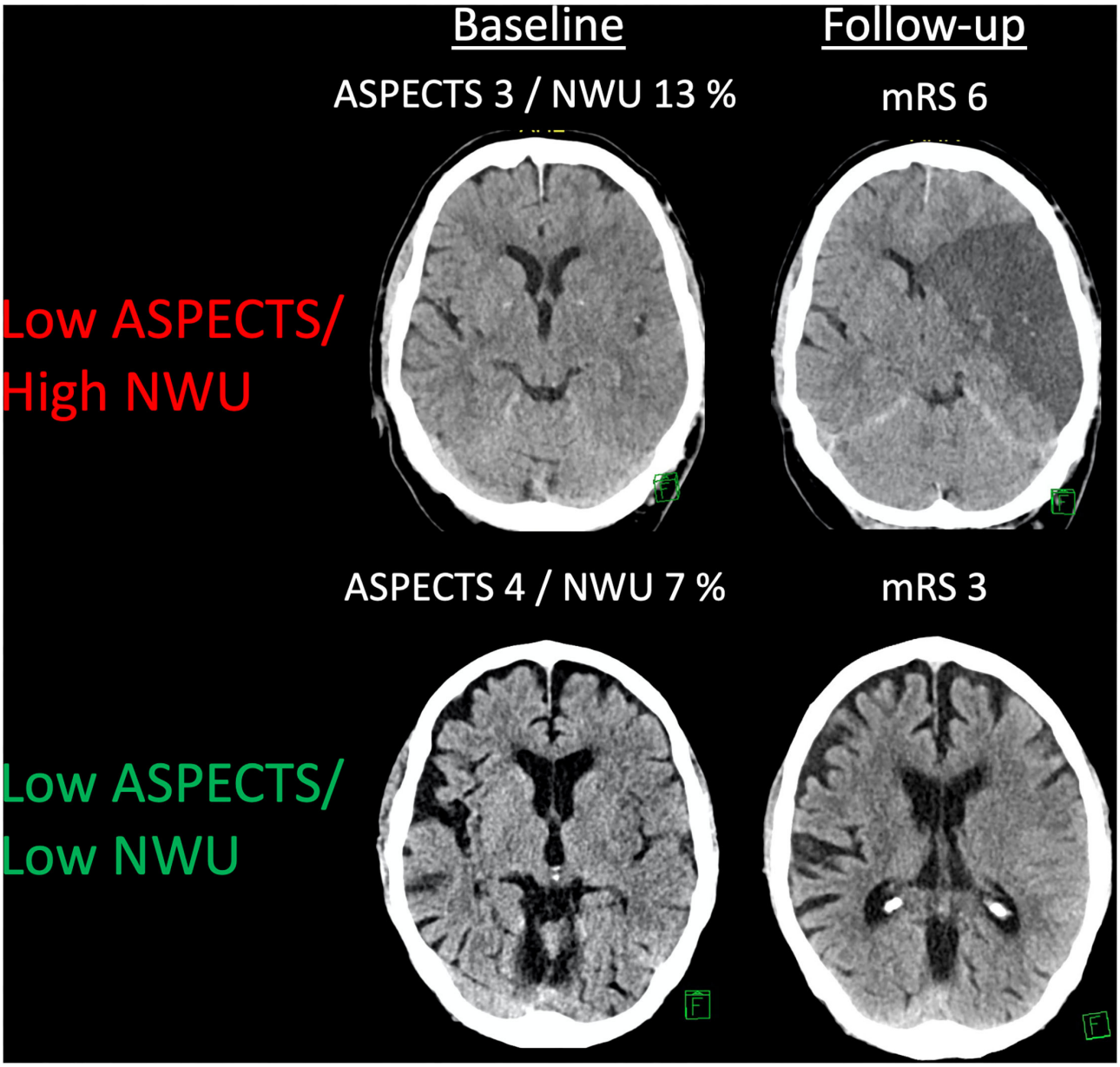


**FIGURE 1 |** An example of patients with low ASPECTS and different kinds of net water uptake (NWU). Two examples showing patients with a low ASPECTS and low or high NWU, respectively. Follow-up imaging and a functional outcome are displayed.

patients achieving functional independence. **Figure 1** illustrates two examples of patients with low ASPECTS with high- vs. low-baseline NWU, respectively. Comparing the baseline NWU in patients with good clinical (mRS 0–2) vs. a poor outcome (mRS 3–6), the median NWU was significantly lower in patients with a good outcome (median 7.6, IQR: 4.6–8.7 vs. median 10.8, IQR: 8.9–13.9; $p < 0.0001$). **Table 1** shows the patient characteristics.

In ROC curve analysis, the highest diagnostic power was observed for NWU (AUC: 0.84; 95% CI: 0.77–0.89; Youden J: 0.59; cutoff, 9.1%; sensitivity, 88.2%; specificity, 70.6%), and ASPECTS (AUC: 0.78; 95% CI: 0.71–0.84; Youden J: 0.54; cut-off, 4; sensitivity, 88.2%; specificity, 65.4%). NIHSS on admission (AUC: 0.73) and age (AUC: 0.68) showed a moderate to low diagnostic ability to classify an outcome (**Table 2**; **Figure 2**). In multivariable logistic regression analysis, age (OR: 0.92; 95% CI: 0.85–0.99; $p = 0.02$), NWU (OR: 0.52; 95% CI: 0.37–0.74; $p < 0.001$), ASPECTS (OR: 17.89; 95% CI: 2.93–108.9; $p = 0.001$), and by trend status of recanalization (OR: 5.05; 95% CI: 0.97–26.5; $p = 0.05$) were significantly associated with a good functional outcome at Day 90 (**Table 3**). There was no significant interaction between NWU (continuous) and recanalization. The corresponding interaction term between

**TABLE 1 |** Patient characteristics.

| Variable | *N* = 155 |
|---|---|
| Age (years)—median (IQR) | 75.0 (66–82) |
| Time from onset to imaging in hours—median (IQR) | 3.8 (2.5–5) |
| NIHSS—median (IQR) | 18 (15–21) |
| ASPECTS—median (IQR) | 4 (3–5) |
| NWU (%)–mean (SD) | 10.8 (3.8) |
| IV rtPA, n (%) | 88 (56.8) |
| Thrombectomy, n (%) | 78 (50.3) |
| successful recanalization (mTICI ≥ 2b), n (%) | 50 (64.0) |
| mRS90 0–2—n (%) | 17 (11%) |

**TABLE 2 |** ROC curve analysis.

| | AUC | 95%CI |
|---|---|---|
| ASPECTS | 0.78 | 0.70–0.84 |
| %—Net Water Uptake | 0.84 | 0.79–0.89 |
| NIHSS on admission | 0.73 | 0.65–0.80 |
| Age | 0.68 | 0.60–0.76 |
| Time from onset—imaging | 0.54 | 0.46–0.63 |

NWU and recanalization status was not statistically significant (OR: 0.85; 95% CI: 0.55–1.29; $p = 0.47$). When replacing the independent variable "recanalization status" with "MT," MT did not show a statistically significant association with an outcome (OR: 1.93; 95% CI: 0.28–13.26; $p = 0.50$).

In multivariable logistic regression analysis with mRS 0-3 as a dependent variable, NWU (continuous) was confirmed as an independent predictor of a good outcome (OR: 0.82; 95% CI: 0.72–0.93; $p = 0.002$), besides ASPECTS (OR: 2.07; 95% CI: 1.09–3.92; $p = 0.03$), and age (OR: 0.95; 95% CI: 0.92–0.99, $p = 0.01$) (**Table 3**).

In patients with NWU > 9.1% (cut-off from ROC curve analysis), successful recanalization did not show a statistically significant association with an improved outcome (OR: 1.17; 95% CI: 0.18–7.56, $p = 0.87$), while recanalization was significantly associated with a good outcome in patients with NWU < 9.1% (OR: 8.46; 95% CI: 1.7–41.1; $p = 0.009$).

## DISCUSSION AND CONSEQUENCES FOR CLINICAL TRIALS

The aim of this pilot study was to investigate the impact of baseline NWU as a quantitative imaging biomarker in the

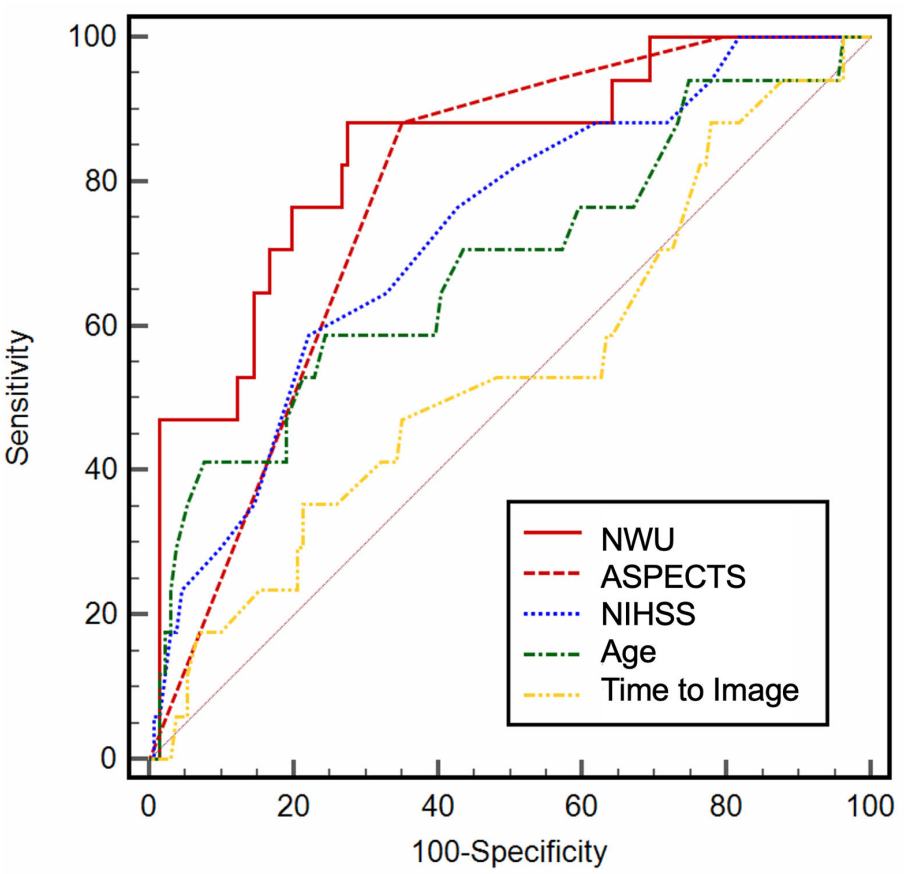


**FIGURE 2 |** Receiver operating characteristic (ROC) curve analysis. ROC curve analysis for baseline variables, illustrating the diagnostic ability.

**TABLE 3 |** Multivariable logistic regression analysis.

| | Modified rankin scale 0–2 | | | Modified rankin scale 0–3 | | |
|---|---|---|---|---|---|---|
| | **OR** | **95%CI** | ***P* value** | **OR** | **95%CI** | ***P* value** |
| NWU | 0.52 | 0.37–0.74 | <0.001 | 0.82 | 0.72–0.93 | <0.01 |
| ASPECTS | 17.89 | 2.93–109 | 0.02 | 2.07 | 1.09–3.92 | 0.03 |
| Age | 0.92 | 0.85–0.99 | 0.02 | 0.95 | 0.92–0.99 | 0.01 |
| Recanalization | 5.05 | 0.97–26.5 | 0.05 | n.s. | n.s. | n.s. |

*n.s., not significant.*

assessment of patients with low ASPECTS. We hypothesized that the degree of hypoattenuation (i.e., water uptake) as a second lesion feature besides lesion extent modified the effect of MT on the functional outcome in patients with low ASPECTS. We observed that NWU was significantly associated with a functional outcome, yielding a higher diagnostic power compared to other parameters, such as ASPECTS, age, or NIHSS.

Yet, no randomized evidence supports MT for patients with low ASPECTS (17). Hence, diagnostic tools are needed to identify the patients with low ASPECTS that are expected to benefit from MT. The ASPECTS rating itself is based on binary subjective rating criteria (hypoattenuation yes/no). It, therefore, does not further quantify the degree of hypoattenuation, a major limitation of ASPECTS as a selection criterion for treatment. The stage of early infarct lesions in brain is defined by NWU, which, in turn, is directly related to lesion hypoattenuation and volume increase (i.e., extracellular edema). The decrease of attenuation of ischemic tissue is directly related to net influx of water, which has been demonstrated *in vitro* and *in vivo* (14, 18, 19). Therefore, an additional quantitative parameter that further stratifies lesion pathophysiology in patients with low ASPECTS could further differentiate the stages of early ischemic changes in acute stroke imaging to exclude those patients that do not benefit from MT (20).

In summary, we observed that neither MT nor successful recanalization after MT was associated with an improved outcome in patients with high NWU, adjusted for baseline ASPECTS. Hence, high NWU at admission may serve as a predictor of futile recanalization. In patients with low ASPECTS but low NWU, recanalization was significantly associated with functional independence. It is important to realize that the current trials investigating MT in patients with low ASPECTS do not consider lesion water uptake (i.e., the degree of hypoattenuation) as a factor for treatment selection, especially considering the extended time window from the symptom onset to imaging in these trials. Patient inclusion in TENSION requires a time from the onset to imaging of <11 h, while both TESLA and SELECT-2 include patients up to 24 h after the symptom onset. Hence, a patient with an ASPECTS of 2, high degree of lesion water uptake, and presenting after up to 24 h after the onset may be randomized in the TESLA trial and undergo MT. According to our data, recanalization of patients with low ASPECTS with high water uptake is not associated with a clinical benefit, and futile MT may occur with high probability. Moreover, ASPECTS remained an independent predictor of an outcome despite preselection of patients (i.e., ASPECTS 0–5 only) with a high OR, which emphasized differences among the lower ASPECTS scale, particularly encouraging treatment of ASPECTS 4–5.

Alternative concepts to patients with triage low ASPECTS are currently discussed, for instance, the utilization of CTP (5). This approach, however, is often criticized, in particular with regard to overestimation of the volume of irreversibly injured tissue, potentially causing the exclusion of patients who might benefit from MT (5, 11, 21). Second, CTP-derived core volumes did not modify the effect of MT on a clinical outcome in a HERMES meta-analysis (22). In contrast, NWU could serve as a quantitative imaging biomarker that specifically represents ischemic edema as a hallmark of irreversible infarction with very low likelihood of reversibility (5, 14, 23).

An approach for a clinical feasible implementation of NWU in the assessment of patients with extensive baseline infarct lesion could be realized by an adjusted ASPECTS. The degree of hypoattenuation per ASPECTS region could be quantified using simple measurements of relative density changes in the ischemic brain tissue compared to a contralateral region of interest and then be used to adjust the ASPECT score. Further studies are needed to validate the impact of NWU in patients with low ASPECTS and to test the applicability and diagnostic ability of an edema-corrected ASPECTS. Limitations of our study include the relatively small number of patients due to strict inclusion criteria. Furthermore, the retrospective design of this study does not allow for valid conclusions regarding treatment effects. Moreover, the matching of patients who did not undergo MT as "not successfully recanalized" might lead to an underestimation of the effect of MT due to the potential phenomenon of spontaneous reperfusion. We did not observe a significant interaction between baseline NWU and recanalization, but this might be biased by the small number of patients. Yet, the quantification of NWU in admission CT requires the utilization of CTP, which is a limitation of this method. Future studies should validate alternative concepts of NWU quantification, for instance, using automated voxel-wise analysis of NECT hypoattenuation per ASPECTS region, or using multiphase CTA maps to define the ROI for NWU quantification in NECT.

## CONCLUSION

In stroke patients with LVO and initial ASPECTS of $\leq 5$, low NWU of early infarct may constitute a beneficial constellation for vessel recanalization. No conclusive evidence of a beneficial effect of successful reperfusion was observed in patients with low ASPECTS and high NWU, which highlights the potential of NWU as a tool to specify patient selection.

## DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available due to ethical restrictions that prevent the sharing of data. Requests

to access the datasets should be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission der Ärztekammer Hamburg. The Ethics Committee waived the requirement of written informed consent for participation.

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## AUTHOR CONTRIBUTIONS

GB, LM, JF, and AK have contributed in conception and design of the study. GB, RM, MB, and AK have contributed in acquisition and analysis of data. GB, UH, JF, and AK have contributed in drafting a significant portion of the manuscript. All authors contributed to the article and approved the submitted version.

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