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Haemorrhage after thrombectomy with adjuvant thrombolysis in unknown onset stroke depends on high early lesion water uptake

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ABSTRACT

Background and purpose In wake-up stroke, CT-based quantitative net water uptake (NWU) might serve as an alternative tool to MRI to guide intravenous thrombolysis with alteplase (IVT). An important complication after IVT is symptomatic intracerebral haemorrhage (sICH). As NWU directly implies ischaemic lesion progression, reflecting blood-brain barrier injury, we hypothesised that NWU predicts sICH in patients who had a ischaemic stroke undergoing thrombectomy with unknown onset.

Methods Consecutive analysis of all patients who had unknown onset anterior circulation ischaemic stroke who underwent CT at baseline and endovascular treatment between December 2016 and October 2020. Quantitative NWU was assessed on baseline CT. The primary endpoint was sICH. The association of NWU and other baseline parameters to sICH was investigated using inverse-probability weighting (IPW) analysis.

Results A total of 88 patients were included, of which 46 patients (52.3%) received IVT. The median NWU was 10.7% (IQR: 5.1–17.7). The proportion of patients with any haemorrhage and sICH were 35.2% and 13.6%. NWU at baseline was significantly higher in patients with sICH (19.1% vs 9.6%, p<0.0001) and the median Alberta Stroke Program Early CT Score (ASPECTS) was lower (5 vs 8, p<0.0001). Following IPW, there was no association between IVT and sICH in unadjusted analysis. However, after adjusting for ASPECTS and NWU, there was a significant association between IVT administration and sICH (14.6%, 95% CI: 3.3% to 25.6%, p<0.01).

Conclusion In patients with ischaemic stroke with unknown onset, the combination of high NWU with IVT is directly linked to higher rates of sICH. Besides ASPECTS for evaluating the extent of the early infarct lesion, quantitative NWU could be used as an imaging biomarker to assess the degree of blood-brain barrier damage in order to predict the risk of sICH in patients with wake up stroke.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In patients who had a ischaemic stroke presenting with an unknown onset of stroke, neuroimaging is required to guide intravenous treatment with alteplase (IVT), as recently investigated in the Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) and Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial. Besides MRI and CT perfusion, quantitative lesion net water uptake (NWU) is a further tool to assess patients with wake-up stroke to estimate lesion age. However, there is yet no data on the potential value of this biomarker in the assessment of patients with wake-up stroke who also undergoes endovascular treatment.

WHAT THIS STUDY ADDS

⇒ The risk of symptomatic intracerebral haemorrhage (sICH) as feared complication in this real-world CT-based cohort of patients with unknown onset stroke undergoing thrombectomy was significantly linked to high lesion NWU and large lesion extent (low Alberta Stroke Program Early CT Score, ASPECTS). In contrast, IVT was not associated with sICH in patients with low NWU or high ASPECTS.

⇒ Patients with higher NWU at baseline received IVT with a similar frequency than patients with low NWU indicating that a more pronounced tissue hypoattenuation does not necessarily influence treatment decision-making for IVT.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The administration of IVT may be safe for patients with wake-up stroke with less pronounced ischaemic changes as indicated by ASPECTS and NWU on admission CT. Quantitative NWU should be tested prospectively as a complementary imaging biomarker to ASPECTS in order to assess the degree of blood-brain barrier damage predicting the risk of sICH particularly in patients who had a ischaemic stroke with unknown onset.

INTRODUCTION

Wake-up stroke occurs in approximately 25% of all patients who had ischaemic strokes, which may lead to an exclusion from thrombolysis with alteplase (IVT).[1] In this context, neuroimaging may be used to

guide IVT, as recently investigated in the Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) and Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial.[2 3] In the WAKE-UP trial, MRI was used to indicate lesion progression in patients with unknown onset stroke.[3] The EXTEND trial used CT perfusion (CTP) to detect patients who had ischaemic stroke with tissue-at-risk suggesting an expected benefit from IVT in the time window of 4.5–9 hours, and in unknown onset stroke.[2] Yet, MRI and automated CTP imaging tools are not always available in every stroke centre. A further tool to assess patients with wake-up stroke is quantitative lesion net water uptake (NWU), a CT-based imaging biomarker that may be applied to assess lesion age.[4 5] All methods estimate the degree of lesion progression to enable treatment with different pathophysiological approaches. In cases of a more pronounced lesion progression (ie, no mismatch on diffusion-weighted imaging to fluid-attenuated inversion recovery (DWI-FLAIR), large core volume without penumbra, respectively), the administration of IVT is associated with a higher risk of secondary haemorrhage leading to futile treatment with worse outcomes, and is therefore withheld from these patients. The main advantage of quantitative NWU besides its rapid assessment is its quantitative nature. Hence, the degree of NWU at baseline in patients with wake-up stroke could be used to estimate risk for secondary injury volumes following treatment, particularly symptomatic intracerebral haemorrhage (sICH). However, there is yet no data on the potential value of this biomarker in the assessment of patients with wake-up stroke who also undergoes endovascular treatment. The aim of this study was to assess the relationship of CT-based quantitative NWU and the occurrence of sICH. We hypothesised that (1) NWU is a predictor of sICH in patients presenting with large vessel occlusion and unknown onset and (2) NWU modifies the risk of sICH for patients receiving IVT.

METHODS

Patients

The local high-volume university hospital stroke registry was screened consecutively to select all patients with anterior circulation ischaemic stroke admitted between December 2016 and April 2020 who received multimodal CT imaging at baseline. Only anonymised data was analysed following review of the ethics committee. Informed consent was waived. Inclusion criteria that were used to screen patients were: (1) ischaemic stroke with occlusion of the middle cerebral artery or distal occlusion of the internal carotid artery without affected anterior or posterior cerebral artery territory; (2) CT imaging on admission including non-enhanced CT (NECT), CT-angiography to confirming vessel occlusion, CTP; (3) unknown onset of stroke; (4) mechanical thrombectomy (MT) procedure performed; (5) no intracranial haemorrhage or old demarcated infarctions on baseline CT.

There were individual reasons for IVT administration despite an unknown onset of stroke. In this context, the baseline Alberta Stroke Program Early CT Score (ASPECTS) was not a definite exclusion criterion. The patient cohort hence included patients with low ASPECTS based on individualised treatment decision-making. Reasons for treatment included a younger age, a favourable imaging pattern on multimodal CT imaging (ie, lower core volume) or specific request for treatment by family members.

ASPECTS were deducted from the clinical documentation. All reported ASPECTS were validated by an experienced board-certified attending neuroradiologist (>10 years of experience) in the local imaging core laboratory. Follow-up imaging was scanned for any secondary intracerebral haemorrhage (ICH). The primary outcome was sICH defined according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) protocol as parenchymal haemorrhage type 2 on the 22–36-hour post-treatment imaging scan, combined with a neurological deterioration of 4 points or more on the National Institute of Health Stroke Scale (NIHSS) from baseline, or from the lowest NIHSS value between baseline and 24 hours, or leading to death.[6] The screening for secondary haemorrhage on follow-up imaging was performed by a board-certified neuroradiologist blinded to clinical data. Functional independence was defined using modified Rankin Scale (mRS) scores of 0–2 at day 90. The mRS scores were evaluated by a physician or a trained and certified neurology study nurse and the readers involved in this study were blinded to clinical data.

Image analysis

Anonymised images were analysed using commercially available software at the local imaging core laboratory (Analyze V.11.0, Biomedical Imaging Resource, Mayo Clinic, Rochester, Minnesota, USA). Quantitative NWU within the early ischaemic lesion was assessed using established CT-densitometry as described and validated before.[4 5] This method is based on the physical relationship between lesion hypodensity and volumetric change due to progressive tissue water uptake over time.[4 7–10] The core lesion for density measurement ($D_{ischaemic}$) was operationally defined as the early hypoattenuated lesion on NECT. Cerebral blood volume maps were presented simultaneously to improve the precision of the region of interest (ROI) definition. The ROI defining the density of the ischaemic core ($D_{ischaemic}$) was then mirrored symmetrically to the contralateral hemisphere to assess the physiological density of brain tissue prior to infarction (D_{normal}). The segmentation of the ROIs was performed with semiautomatic edge detection and a sampling with the Hounsfield units (HU) preset range of 20–80. NWU was then calculated according to $D_{ischaemic}$ and D_{normal} (equation 1).

Equation 1[4 7]:

$$\%\ \text{water uptake} = \left(1 - \frac{D_{ischaemic}}{D_{normal}}\right) \times 100.$$

Statistical analysis

Shapiro-Wilk tests were used to test for normal distribution. Continuous variables are presented as means and 95% CIs or medians and IQRs and Student's t-test and Mann-Whitney U tests were used to test for group differences. Categorical variables were compared using χ^2 tests. The association of baseline clinical and imaging parameters as well as treatment variables to sICH was tested using inverse-probability weighting (IPW) with a doubly robust method combined modelling of the treatment and logit outcome (sICH) with robust SE type and 1e−5 tolerance for overlap assumptions analysis with and without implementing age, NIHSS, ASPECTS, NWU, recanalisation status and application of intravenous alteplase as covariates. Correlation between all independent variables was assessed to test for multicollinearity. The estimated average treatment effect of IVT was also calculated for dichotomised ASPECTS (defined by the median) and NWU subgroups. We applied an a priori defined NWU threshold of 11.5% as established optimal cut-off to dichotomise ischaemic lesions with high and low NWU. Accordingly, lesion age was defined as above or below 4.5 hours. To illustrate the relationship of NWU, ASPECTS and risk for sICH, we used a multivariable logistic regression model with IPW-weights showing the marginal means for NWU and (dichotomised) ASPECTS. Finally, the area under the curve (AUC) was determined for ASPECTS and NWU in binary receiver operating characteristic (ROC) curve analysis. To directly compare the diagnostic accuracy of ASPECTS versus NWU to classify sICH, two multivariable logistic regression models were compared, both models consisting of age, NIHSS and application of IVT including either ASPECTS or NWU. A statistically significant difference was accepted at a p value of <0.05. Analyses were performed using Stata V.17.0 (StataMP, StataCorp, Texas, USA).

Data availability statement

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

RESULTS

Characteristics of the study population

Eighty-eight patients were included. The main patient characteristics can be found in table 1. The median age was 78 years (IQR: 67–85) and the median NIHSS was 17 (IQR: 11–20). The median ASPECTS was 8 (IQR: 6–8). The median number of retrievals was 2 (IQR: 1–2) and 71 patients (81%) showed a modified thrombolysis in cerebral infarction (mTICI) 2b–3 at the conclusion of the procedure. The median NWU was 10.7% (IQR: 5.1%–17.7%). Forty-one patients (47%) showed high NWU at

Table 1 Patient characteristics

Baseline characteristics	No ICH	ICH (except sICH)	sICH	P value*
Subjects, n (%)	56 (64)	20 (22)	12 (14)	
Baseline variables				
Age in years, median (IQR)	79 (65–86)	76 (67–83)	78 (77–83)	0.90
Female sex, n (%)	26 (47)	13 (65)	7 (58)	0.52
Arterial hypertension, n (%)	26 (46)	10 (48)	5 (40)	0.36
Cardioembolic aetiology, n (%)	35 (62)	9 (45)	5 (40)	0.14
Prior anticoagulation or antiplatelet therapy, n (%)	31 (55)	12 (60)	2 (17)	0.36
Admission NIHSS, median (IQR)	16 (9–19)	17 (13–21)	17.5 (14–20)	0.36
ASPECTS, median (IQR)	8 (7–9)	6 (5–7)	5 (5–7)	<0.001
NWU, median (IQR)	9.1 (3.0–14.1)	10.3 (8.3–22.6)	18.8 (16.2–27.9)	0.007
Treatment and endpoints				
IVT administration, n (%)	29 (52)	16 (80)	9 (75)	0.09
mTICI 2b/3, n (%)	46 (82)	15 (77)	9 (75)	0.59
Number of passes, median (IQR)	2 (1–2)	1 (1–3)	1 (1–1)	0.62
NIHSS at 24 hours, median (IQR)	15 (8–20)	18 (11–23)	24 (19–42)	0.15
mRS 0–2, n (%)	20 (36)	3 (15)	1 (8.3)	0.008
mRS, median (IQR)	4 (2–5.5)	5 (3–6)	5.5 (3.5–6)	0.03

*Group comparison of patients with ICH versus without ICH.
ASPECTS, Alberta Stroke Program Early CT Score ; FUCT, follow-up computed tomography; ICH, intracerebral haemorrhage; IVT, intravenous thrombolysis with alteplase; mRS, modified Rankin Scale; mTICI, modified Thrombolysis In Cerebral Infarction; NIHSS, National Institute of Health Stroke Scale; NWU, net water uptake; Pr, Probability; sICH, symptomatic ICH.

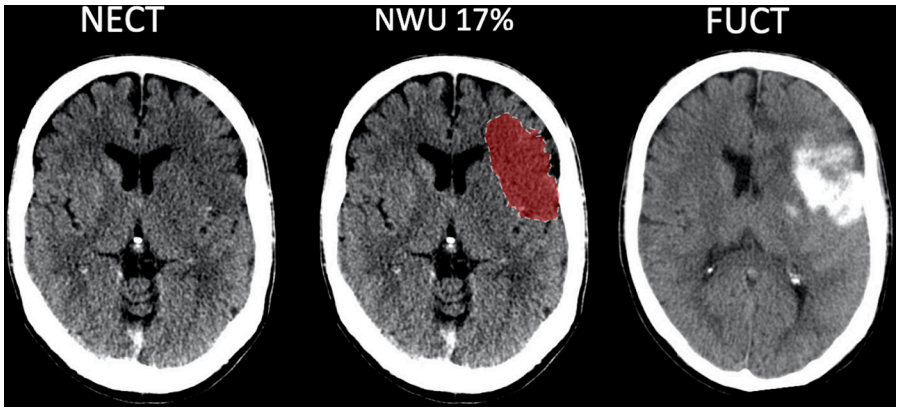

Figure 1 Case illustration. Patient with ischaemic stroke due to proximal middle cerebral artery occlusion left, the ASPECTS was 6, quantitative NWU was 17%. Patient received intravenous alteplase and underwent successful endovascular recanalisation with mTICI 2c. Symptomatic intracerebral haemorrhage occurred 24 hours after thrombectomy. NECT, non-enhanced CT; NWU, net water uptake.

baseline (>11.5%). After 24 hours, the median NIHSS was 15 (IQR: 8–21), and 8 (IQR: 2–16) at discharge. At day 90, the median mRS was 4 (IQR: 2–6) with 23 patients (26%) achieving functional independence (mRS 0–2). Thirty-one patients (35.2%) showed any ICH at follow-up and 12 patients (13.6%) showed sICH. Figure 1 illustrates an example of a patient with high NWU. Figure 2 shows a flow chart of patient inclusion.

Comparing patients with any secondary ICH to patients without, the median NWU was higher (16.0% vs 9.3%, p=0.007), and the median ASPECTS was lower in patients with ICH (6 vs 8, p<0.001). Age and admission NIHSS were similar. There were no significant differences regarding treatment (application of alteplase, recanalisation status and number of retrievals). Patients with ICH had a higher mRS at day 90 (5 vs 4, p=0.03), and achieved functional independence less frequently (10% vs 36%, p=0.008). The occurrence of sICH was associated with poor functional outcome (8.3% of patients with sICH and functional independence at day 90 vs 28.9% in patients without sICH). When using the established NWU threshold of 11.5% to group patients into patients with high versus low NWU, significant differences were observed regarding the rate of sICH, which was 18.0% for patients with high NWU versus 2.3% for patients with low NWU (p=0.01). The rate of IVT administration was not different when comparing patients with high versus low NWU (45% vs 59%, p=0.2) (table 2). Fifty patients did not take any anticoagulation or antiplatelet drugs. Twenty patients had aspirin in their medication list, 14 patients took factor Xa inhibitors for anticoagulation therapy and 4 patients were on enoxaparin sodium. The rate of sICH according to these subgroups were 24% (no medications), 10% (aspirin), 0% (Xa) and 0% (enoxaparin), which was not statistically different (p=0.08).

Inverse-probability weighting

In unadjusted IPW analysis, the effect of IVT administration, degree of NWU (binarised, cut-off: 11.5%) and ASPECTS (binarised, low vs high, cut-off: 6) on the occurrence of sICH were analysed. The average treatment effect of IVT on the occurrence of sICH was +12.4% (95% CI: −0.1% to 26.3%), which was not significant (p=0.08). Low ASPECTS (+21.9%, 95% CI: 4.0% to 39.8%; p=0.02) and high NWU (+22.7%, 95% CI: 9.2% to 36.3%, p<0.01) were significantly associated with higher probability of sICH.

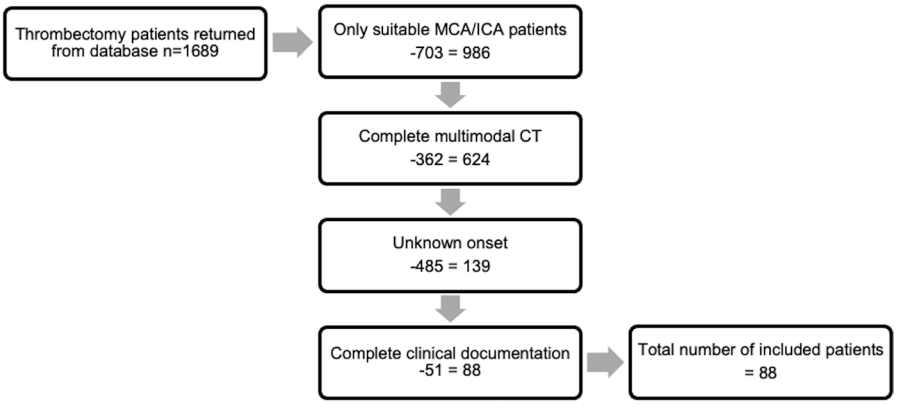

Figure 2 Flow chart of patient inclusion. NWU, net water uptake; sICH, symptomatic intracerebral haemorrhage.

Table 2 Functional outcome and rate of symptomatic intracranial haemorrhage for patients with IVT versus without IVT according to the degree of NWU (binarised)

(A) mRS at day 90	Low NWU	High NWU	P value
IVT	3 (IQR: 1–6)	5 (IQR: 4–6)	0.02
No IVT	3 (IQR: 2–4)	5 (IQR: 3–6)	0.01
P value	0.88	0.41	
(B) % sICH			
IVT	0	38	0.04
No IVT	0	13	0.16
P Value	0.22	0.05	

IVT, intravenous thrombolysis with alteplase; mRS, modified Rankin Scale; NWU, net water uptake; sICH, symptomatic intracerebral haemorrhage.

Second, the effect of IVT on sICH was analysed including NWU, ASPECTS, age and NIHSS as covariates. Using this model, IVT was significantly associated with sICH (+16.8%, 95% CI: 5.3% to 28.4%, p<0.01). In the subgroup of patients with high NWU (>11.5%), the effect of IVT on sICH was also significant with a higher coefficient compared with all patients (+36.1%, 95% CI: 11.2% to 61.0%, p<0.01) (table 3). Similarly, the effect of IVT on the occurrence of sICH was pronounced in the subgroup of patients with a low ASPECTS of ≤6 (+48.2%, 95% CI: 23.8% to 72.5%, p<0.001). In contrast, the administration of IVT in the subgroup of patients with low NWU and high ASPECTS was not associated with sICH (+4.9% and +3.4%, p=0.34 and p=0.30).

These observations were confirmed by multivariable logistic regression analysis. Both NWU (adjusted OR (aOR): 1.09, 95% CI: 1.01 to 1.18, p=0.03) and ASPECTS (aOR: 0.04, 95% CI: 0.003 to 0.6, p=0.02) were independent predictors of sICH. The diagnostic accuracy to classify the presence of sICH based on a bivariate model consisting of NWU and ASPECTS was 0.77. Table 4 illustrates the increasing probability for sICH according to baseline NWU adjusted for baseline and treatment variables. While the probability was 4.5% for a lesion with 5% NWU, the risk increased to 10.2% for a lesion with 15% NWU, and to 14.8% for a lesion with 20% NWU. Figure 3 illustrates the relationship of NWU and ASPECTS for the prediction of sICH.

Table 3 Inverse-probability weighting (IPW) analysis to show the effect of IVT, NWU and ASPECTS on sICH

sICH	ATE	95% CI	P value
IVT (unadjusted)	+12.4%	−0.14 to 26.3	0.08
IVT (adjusted*)	+16.8%	5.3 to 28.4	<0.01
Low ASPECTS (median)	+9.8%	−0.05 to 24.3	0.03
High NWU (median)	+17.5%	4.9 to 30.1	<0.01
IVT in high NWU	+36.1%	11.2 to 61.0	<0.01
IVT in low ASPECTS	+48.2%	23.8 to 72.5	<0.001
IVT in high ASPECTS	+4.9%	−0.05 to 15.0	0.34
IVT in low NWU	+3.4%	−0.03 to 9.97	0.30

*Adjusted for age, NIHSS, NWU, ASPECTS and recanalisation status.
ASPECTS, Alberta Stroke Program Early CT Score; ATE, average treatment effect; IVT, intravenous thrombolysis with alteplase; NIHSS, National Institute of Health Stroke Scale; NWU, net water uptake; sICH, symptomatic intracerebral haemorrhage.

Table 4 Probability for functional independence at day 90 and symptomatic intracranial haemorrhage according to the degree of baseline NWU based on multivariable logistic regression analysis

% NWU at baseline	Probability for mRS 0–2*	Probability for sICH*
5	29.6%	4.5%
10	27.0%	6.8%
15	24.4%	10.2%
20	22.0%	14.8%
25	19.8%	20.9%
30	17.8%	28.7%
35	15.9%	38.0%

*Adjusted for age, NIHSS, ASPECTS, IVT and recanalisation status.
ASPECTS, Alberta Stroke Program Early CT Score; ICA, Internal Carotid Artery; IVT, intravenous thrombolysis with alteplase; MCA, Middle Cerebral Artery; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; NWU, net water uptake; sICH, symptomatic intracerebral haemorrhage.

Model comparison NWU versus ASPECTS

In univariable ROC analysis, the AUC for ASPECTS to classify sICH was 0.82 and the AUC for NWU was 0.84. The optimal cut-off for NWU to classify sICH was 15.8% (accuracy 77.3%, sensitivity 91.7% and specificity 75.0%) defined as the NWU value with the highest Youden Index. The AUC of the other available variables were <0.7. Comparing both multivariable logistic regression models, the AUC for the ASPECTS model was 0.84, and the AUC for the NWU model was 0.93.

DISCUSSION

This observational study investigating the value of quantitative NWU in the assessment of patient who had a stroke with unknown time window undergoing endovascular treatment revealed the following main findings: (1) the rate of sICH as feared complication in this real-world CT-based cohort of patients undergoing thrombectomy was 13.6%, and NWU and ASPECTS at baseline were significant predictors, (2) patients with higher NWU at baseline received IVT with a similar frequency than patients with low NWU indicating that a more

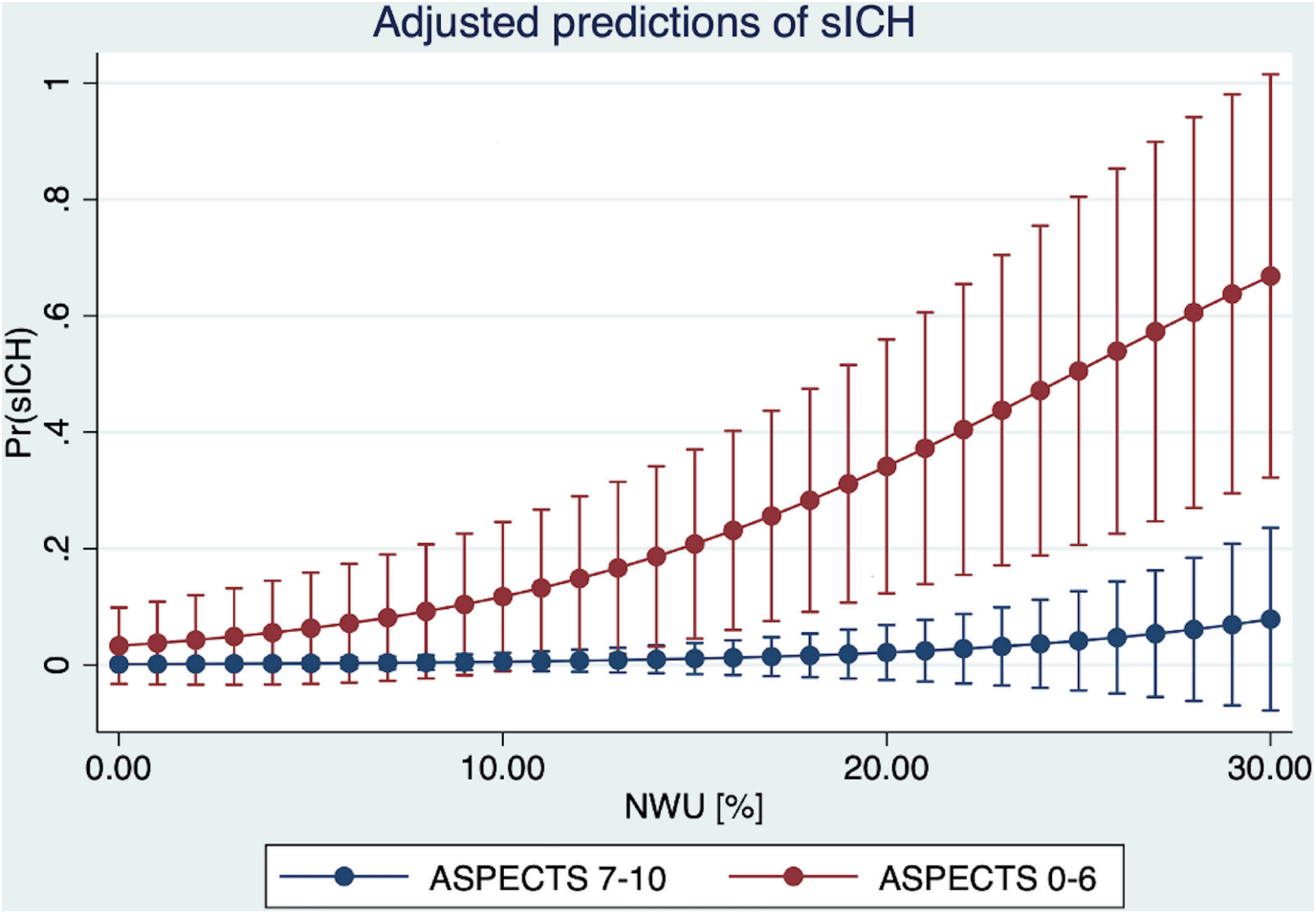

Figure 3 Multivariable logistic regression analysis to predict symptomatic intracerebral haemorrhage (sICH). Probability for sICH according to the baseline net water uptake differentiated for high versus low ASPECTS patients.

pronounced tissue hypoattenuation does not necessarily influence treatment decision-making for IVT, (3) The risk of sICH increased significantly in patients receiving IVT with high NWU or low ASPECTS, while IVT was not associated with sICH in patients with low NWU or high ASPECTS. Hence, the administration of IVT may be safe for patients with wake-up stroke with less pronounced ischaemic changes as indicated by ASPECTS and NWU on admission CT. Thirty-nine patients (44%) had low NWU and high ASPECTS, and there were not patients with sICH in this subgroup independent from IVT administration or degree of reperfusion after thrombectomy.

To our knowledge, this is the first observational study of patients with unknown onset stroke who underwent CT imaging and thrombectomy observing a potential value of quantitative NWU for acute imaging triage. Our stroke cohort consisted of large vessel occlusions with thrombectomy reflected by the median NIHSS of 17, which was significantly higher than the median NIHSS of 6 in the WAKE-UP cohort. For likely the same reason, our study showed a comparably higher rate of sICH (13.6%). Moreover, one-third of the patients had a low ASPECTS of 0–6, which is known to be directly linked to the occurrence of ICH after IVT.[11–14] In contrast, the median baseline (DWI) core volume in the WAKE-UP cohort was 2 mL.[3] The median quantitative NWU in this study was 10.7% which was similar to study of Minnerup *et al* (ie, 11.5%).[4] This cut-off has been described and subsequently validated to be the optimal cut-off to distinguish a lesion age below or above of 4.5 hours. This study further shows that a high proportion of patients with unknown onset of stroke have low NWU indicating a lower degree of lesion progression and hence a beneficial constellation for IVT administration. As illustrated in table 4, the risk of sICH significantly and unidirectionally increased with higher NWU. 5% NWU well corresponds to an early lesion with subtle hypodensity (risk of sICH: 4.5%). 10% NWU corresponds to a lesion age of approximately 4.5 hours (risk of sICH: 6.8%) and 15% represents a fairly visible lesion on NECT (risk of sICH: 10.2%). Still, the median NWU for patients receiving IVT was 9.9% (IQR: 5–16) illustrating that IVT is often administered in unknown onset patients despite a visible lesion on NECT subsequently being linked to sICH.

According to the current guidelines, advanced CTP imaging (ie, penumbral imaging using automated software tools), or MRI is required to enable thrombolytic and endovascular treatment in patients with unknown onset

of stroke.[11 12] However, both MRI and automated CTP tools are not always available, which emphasises the need for alternative diagnostic tools to estimate lesion progression for treatment selection and outcome prediction. Supporting this, a recent analysis observed that NECT alone might be similarly suitable as imaging modality for the assessment of patients with extended time window stroke; a cohort which is similarly characterised by the need for advanced imaging to enable treatment.[13 14] The quantification of NWU might serve as complementary or alternative tool, which may be obtained by NECT only, although the current published standardised measurement procedure includes CTP to guarantee a precise definition of the core lesion for density measurements. This step could be replaced by automated voxel-wise algorithms that are already available (ie, for instance analogous to tools for automated ASPECTS calculation[15]) and might improve the precision and applicability of NWU.[16–18] A main advantage of quantitative NWU besides its straightforward assessment is its quantitative nature that directly correlates with infarct progression. In contrast, DWI-FLAIR mismatch constitutes a subjective binary screening tool. Penumbral imaging with threshold-based estimation of tissue viability oversimplifies the complexity of pathophysiological processes (ie, switch-like classification of voxels into 'infarct' and 'no infarct').

NWU is directly correlated with degree of hypoattenuation, which is already considered a visual cue in treatment decision-making. The American Stroke Association / American Heart Association (ASA/AHA) guidelines state that the administration of alteplase is recommended in the setting of 'mild to moderately' extensive early ischaemic changes on CT but should not be administered to patients showing extensive regions of 'clear hypoattenuation'.[19] However, no specific thresholds are stated regarding the extent of ischaemic changes (eg, ASPECTS threshold), or regarding the degree of hypoattenuation that defines 'clear hypoattenuation'. In line with this, the rate of IVT administration in this patient cohort was not different when comparing patients with high versus low NWU emphasising that the degree of hypoattenuation is currently not used in imaging triage of patients with wake-up stroke.

Recently, the MissPerfeCT study tested whether a CT hypoperfusion-hypodensity mismatch may identify patients with ischaemic stroke within 4.5 hours of symptom onset as a method to enable thrombolytic treatment in patients with wake-up stroke without using automated CTP imaging tools or MRI. The rationale behind this study was to identify patients with lower infarct progression, defined by evident hypoperfusion but absent hypoattenuation (= net water uptake as indicator of vasogenic oedema and therefore irreversible tissue injury). Still, the question remains whether IVT may be administered safely in patients with wake-up stroke showing tissue hypodensity.[20]

The presence and the extent of early ischaemic changes for treatment selection is a major topic in stroke research and highly relevant in the context of endovascular treatment and IVT. ASPECTS and NWU reflect both dimensions of lesion progression in early stroke CT. While ASPECTS is used as an estimator of the lesion extent, NWU might be interpreted as indicator of 'ischemia depth' per volume, which has been described as precise tool to determine irreversible tissue injury.[21] In the past, it has been observed that the extent of hypoattenuation was predictive of the clinical response to IVT.[22] Second, a low ASPECTS has been linked to higher rates of sICH following IVT[23] or MT.[24] Third, the degree of hypoattenuation reflecting NWU, has been discussed as important variable in the assessment of low ASPECTS patients.[15] Currently, prospective trials evaluate the effect of MT in the setting of low ASPECTS.[16 17] It is worth noting that IVT may be applied in these patients before MT, although the effect of IVT for lower ASPECTS is ambiguous.[18 19] As illustrated in figure 3, the risk of sICH is significantly associated with the level of NWU at baseline in patients with a lower ASPECTS, while the risk for sICH was generally low for patients with a higher ASPECTS of 7–10. While low NWU may be a beneficial constellation for intravenous thrombolysis, high levels of NWU may suggest higher lesion progression with more fragile ischaemic tissue and subsequent higher risk for sICH.[8 25]

In summary, these results suggest that sICH and functional outcome are significantly associated with the degree of early ischaemic changes as indicated by ASPECTS and NWU and therefore, the degree of hypoattenuation should be considered in wake-up stroke treatment decision-making, besides ASPECTS. As illustrated in table 4, the association between NWU at baseline and risk of sICH was nearly linear; however, no linear association between NWU and functional recovery was observed. This may be partly caused by the definition of the endpoint itself. The occurrence of sICH might still lead to functional independence at day 90, although with lower odds. Increasing NWU may therefore be particularly relevant in the acute phase, including risk of sICH, while changes on the mRS score at day 90 may be evident in only granular steps (eg, NWU 10–>20%, probability for mRS ≤2 reduces by 30% while risk of sICH doubles).

Quantitative NWU could serve as an easily implementable biomarker in the assessment of patients with unknown onset, serving as a tool to estimate the 'lesion clock' besides ASPECTS. NWU may serve as an additional indicator in penumbral imaging in ambiguous constellations with absent or borderline mismatch volume for patients with unknown or extended time window. The baseline NWU in this patient cohort showed significant variations (IQR 5.1–17.7%). This individual variability may imply an intrinsic limitation to demonstrate the accurate 'time clock', however, also represents an advantage of this method: NWU as an imaging biomarker of the true ischaemic pathophysiology and hence as a patient-specific tool to assess the real 'tissue clock' of lesion progression which us directly related to clinical outcome.[8] Second, in contrast to the MRI signal, the

density in CT is standardised and intrinsically quantitative between different CT scanners by calibration to the attenuation coefficient of water.[4 26] A further advantage of using a CT-based method in acute stroke diagnosis is the comparably better availability, applicability and speed. Hence, combining ASPECTS and NWU assessment on admission imaging should be tested as a tool to screen patients with wake-up stroke, but might also be tested to guide the application of IVT in uncertain indications (ie, bridging vs direct MT). In this context, lower ASPECTS with higher NWU might be in favour of direct MT.[18 19 27 28]

The main limitation of this study is the small number of patients as well as its retrospective design. Still, when comparing patients with versus without sICH, baseline and treatment characteristics including age, NIHSS and status of vessel recanalisation were very similar, while ASPECTS and NWU showed significant differences, hence encouraging further confirmatory studies including more patients to validate these findings. The association of NWU and ASPECTS with asymptomatic ICH has not yet been assessed although a potential clinical relevance has been observed.[29] No patients without thrombectomy were analysed in this study. Moreover, the impact of prior anticoagulation or antiplatelet therapy prior to stroke needs further investigation particularly in light of the recent discussion on benefit versus harm of an off-label utilisation of IVT in patients with anticoagulation treatment.[30] A further issue is the currently limited applicability of NWU assessment in clinical routine, which yet requires manual post processing. Future studies could test automated algorithms to prospectively quantify NWU in the setting of acute stroke triage.[26 31] Despite limitations, we believe our data show a signal for haemorrhagic risk depending on lesion size (ie, ASPECTS) and state of infarct (ie, degree of NWU). Moreover, the results are plausible with respect to known pathophysiology of ischaemic stroke: it is conceivable that larger more hypodense ischaemic lesions in CT convey tissue fragility and will show a higher rate of haemorrhage after mechanical reperfusion compared with smaller lesions with faint hypodensity.

Conclusion

A higher degree of baseline NWU was associated with an aggravated risk of sICH following administration of IVT in patients who had a stroke with unknown onset. Quantitative NWU might serve as a biomarker to indicate ischaemic tissue injury assessing the risk of sICH in patients with unknown onset stroke, particularly in cases with ASPECTS <7.

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