Non-Contrast CT in Place of MRI Mismatch in the Imaging Triage of Acute Ischemic Stroke Patients

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ABSTRACT

Purpose: To determine if attenuation on Non-Contrast Computed Tomography (NCCT) is similar to MRI Diffusion-weighted Imaging (DWI) - Fluid Attenuation Inversion Recovery (FLAIR) mismatch paradigm in predicting the onset time of acute ischemic stroke.

Methods: Data are from the Keimyung Stroke Registry. Patients with anterior circulation occlusion on baseline CT-angiography, known symptom onset time and MRI within 60 minutes of baseline CT were included. All patients received revascularization therapy. Baseline MRI DWI-FLAIR mismatch, hypoattenuation on baseline NCCT and parenchymal hemorrhage (PH) on follow-up imaging were assessed by consensus. To measure the Hounsfield Units (HU) a region of interest (ROI) was placed in the NCCT to correspond to the DWI lesion, a second identical ROI was placed in the normal contralateral parenchyma. A Ratio of ipsilateral divided by contralateral NCCT Hounsfield Unit (rCT) within baseline DWI lesion was calculated. Statistical methods were used to assess if CT hypoattenuation was a reliable biomarker of time from stroke symptom onset and if it compared well with DWI-FLAIR mismatch in predicting PH at 24 hours.

Results: Of 127 patients included [median age 68 (IQR-15), 53.5% male, median onset to MR time 158 (94) minutes], DWI-FLAIR mismatch was seen in 85/127 (67%). NCCT hypo-attenuation was seen in 111/127 (87%). A statistically significant negative correlation was noted between rCT and stroke symptom onset to MRI time (Spearman's $r = -0.33$, $p<0.001$). A rCT > 0.87 best predicted the presence of DWI-FLAIR mismatch [c statistic = 0.84 (95% CI 0.77-0.91), sensitivity 73.75% (95%CI 62.71%-82.95%); specificity 76.92% (95%CI 60.67-88.87%)]. Models with CT hypoattenuation were similar to a model with DWI-FLAIR mismatch in ability to discriminate PH ($p>0.5$).

Conclusion: Degree of hypoattenuation on NCCT can be used in place of DWI-FLAIR mismatch to identify patients with wake up strokes or unknown time of onset.

1. Introduction:

Acute ischemic stroke-on-awakening or with unknown time of onset constitutes 10-27% of all ischemic strokes (1-4). Since current guidelines on intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) restricts use to a 4.5 hour time window, these patients do not get thrombolysed (5) (6). This has evoked interest in identifying imaging characteristics in this group of patients which would potentially help ascertain the time of onset of stroke symptom.

Currently, Magnetic Resonance (MRI) Diffusion-weighted Imaging (DWI)-Fluid Attenuation Inversion Recovery (FLAIR) mismatch has been identified as an important imaging parameter to predict stroke onset time in patients with stroke-on-awakening or those with unknown time of onset (7) (8) (9). A recent study has shown that in the setting of an acute ischemic stroke, the lesion may be appreciable on the MRI DWI sequence within 3 minutes, but it does not show up on the FLAIR sequence for up to 3 hours (10). The lesion evolves and becomes appreciable on the FLAIR sequence within a 3 – 6 hour window, at which point the sensitivity of FLAIR in identifying DWI positive lesions reaches 100%. Based on this understanding that a MRI DWI FLAIR mismatch (absence of FLAIR changes in the presence of DWI changes) may suggest patients presenting early from stroke symptom onset, patients with stroke-on-awakening or unknown time of onset have been safely treated with intravenous thrombolysis (11-13). However, getting an MRI in the acute stroke setting can be challenging (14). In comparison, a non-contrast CT (NCCT) scan is easily available and information on early ischemic changes can be rapidly acquired from it. CT attenuation values start decreasing in the ischemic area as early as 2 hours from the onset of ischemia, and continue to progressively decrease with increasing time (15) (16).

This study compared the degree of hypoattenuation within regions of early

ischemic change on baseline NCCT in patients with ischemic stroke and known time of onset to DWI-FLAIR mismatch on baseline MRI. It tested if degree of hypoattenuation on NCCT head is equivalent to MRI DWI-FLAIR mismatch in ability to determine stroke symptom onset time. It also tested if hypoattenuation on NCCT predicts parenchymal hemorrhage at 24-hours in a similar manner to MRI DWI-FLAIR mismatch.

2. Methods:

Patients:

Data is from the Keimyung Stroke Registry, an ongoing single centre, prospective cohort study of acute ischemic stroke patients presenting to the Keimyung University Hospital, Daegu, South Korea. Details of the registry are described in previous published papers (17, 18). Included patients had a disabling acute ischemic stroke (NIHSS $\geq$ 8) with known time of onset, a baseline NCCT, an anterior circulation occlusion evident on CT Angiography and an MRI performed within 60 minutes from the baseline NCCT. All patients received revascularization therapy (intravenous tPA and/or endovascular thrombectomy). Patients with posterior circulation strokes were excluded from the current analysis. Baseline demographics and clinical characteristics on the patients were obtained.

Imaging acquisition and reading:

All patients included in the study had undergone standard non-helical NCCT scan performed on a multi-slice scanner (Siemens, Forchheim, Germany) using 120 kV, 170 mAs with 5-mm slice thickness. NCCT scan was followed by CT Angiography with a helical scan technique. Coverage was from arch to vertex with continuous axial slices parallel to the orbitomeatal line with 0.6 mm to 1.25 mm slice thickness. Acquisitions were obtained after a single bolus intravenous contrast injection of 90-120 ml non-ionic contrast media into an antecubital vein at 3-5 ml/sec, auto-

triggered by appearance of contrast in a region of interest manually placed in the ascending aorta. Following CT Angiography, these patients underwent MRI scan within 60 minutes. MRI was performed with 1.5T and included axial DWI, Apparent Diffusion Coefficient (ADC), FLAIR, gradient 2D echoplanar sequences along with Time of Flight Angiography (TOF). Parenchymal haemorrhage on the 24-hr NCCT or MRI scan was assessed using the ECASS II criteria (19). All imaging was analysed at the imaging core lab of the Calgary Stroke Program using OsiriX version 4 (http://www.osirix-viewer.com), an image processing software designed for multi-planar reconstruction and volume rendering.

Images were read by a neuroradiologist and a stroke neurologist experienced in stroke imaging. CT and MRI scans from each patient were analysed for the following four parameters:

A) Qualitative Mismatch on MRI: A DWI-FLAIR mismatch was defined by the presence of a DWI lesion (b=1000) without corresponding abnormality on FLAIR. Cases where the FLAIR abnormality was observed in <50% of the DWI lesion were considered FLAIR negative (Figure 1). This definition was used rather than absence of any FLAIR changes as 123/127 (96.9%) patients had at least some FLAIR lesions, although small, within the DWI lesion.

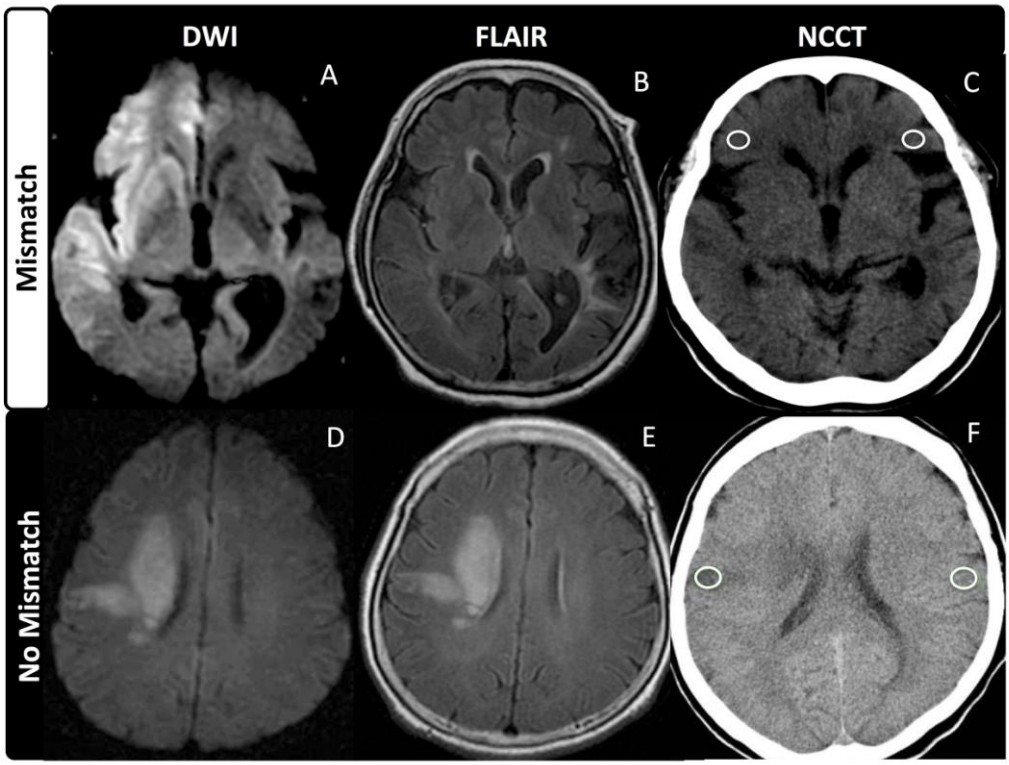

Figure 1: MRI DWI-FLAIR mismatch and no mismatch when compared to NCCT hypoattenuation. Panel A-C shows a patient with mismatch. Panel A shows a DWI lesion without corresponding FLAIR lesion in panel B. NCCT in panel C does not demonstrate any significant hypoattenuation in the ischemic region. rCT (ratio of ipsilateral/contralateral NCCT HU density within the circular mirror ROIs) was 1.02. Panels D-E show a DWI lesion with a corresponding FLAIR lesion. The NCCT in panel F shows severe hypoattenuation in the ischemic region. rCT (ratio of ipsilateral/contralateral NCCT HU density within the circular mirror ROIs) was 0.77.

B) Quantitative Mismatch on MRI: Quantitative (objective) assessment of FLAIR abnormality lesion was done by measuring the signal intensity within a circular region of interest (ROI) on FLAIR, in the region corresponding to the DWI abnormality. These signal intensities were compared to a mirror ROI (reflected on the midline) in the contralateral hemisphere. The resultant ratio was labelled as rFLAIR (ratio of ipsilateral/contralateral FLAIR signal intensity).

C) Qualitative assessment on NCCT: Attenuation on NCCT (as assessed by the experts) was compared qualitatively to NCCT attenuation of the normal contralateral white matter. Infarct density on NCCT scan was then subdivided into 4 groups:

I. **Normal** scan: No hypoattenuation detected by the expert reader.

II. **Slightly hypodense**: Attenuation of infarct same as normal contralateral white matter.

III. **Hypodense:** Attenuation of infarct slightly less than normal contralateral white matter.

IV. **Extremely hypodense** (subacute looking): Attenuation of infarct significantly lower than normal contralateral white matter.

D) Quantitative assessment on NCCT (rCT): The region of DWI abnormality was matched to the NCCT scan visually. Attenuation values (HU) were measured within this region on NCCT scan using a circular ROI. The ROIs were chosen to include cortex and the adjacent portion of subcortical white matter. These ROI attenuation values were then compared to mirror ROIs values in the contralateral hemisphere. The resultant ratio was labelled as rCT (ratio of ipsilateral/contralateral NCCT HU density). (Figure 1).

Care was taken to not include regions with leukoaraiosis in the mirror ROI and the corresponding ipsilesional ROI. Care was also taken to not include regions with wide sulcal spaces, atrophy, and image artifacts into the ROIs.

Statistical analysis:

Standard descriptive statistics was used to compare patients with MRI DWI-FLAIR mismatch and those without. The Fischer's exact test was used to compare qualitative NCCT hypoattenuation with MRI DWI-FLAIR mismatch. Since the variables rCT, rFLAIR and stroke symptom onset to MR time were not distributed normally (Shapiro Wilk test of normality $p < 0.05$), non-parametric Spearman's rank test was used to test for correlation between rCT (ratio of

ipsilateral/contralateral NCCT attenuation density) and rFLAIR (ratio of ipsilateral/contralateral FLAIR signal intensity) and between rCT and stroke symptom onset to MRI time. Receiver Operating Curve (ROC) analysis and the Youden's method were used to identify the optimal rCT threshold predicting presence or absence of MRI DWI-FLAIR mismatch. The De Long method was used to compare logistic regression models with 1) rCT dichotomized at the optimal rCT threshold as predictor variable 2) qualitative CT hypoattenuation dichotomized as normal to slightly hypodense (groups I and II) vs. hypodense to subacute looking (groups III and IV) to the model with MRI DWI-FLAIR mismatch as predictor variable in ability to discriminate parenchymal hemorrhage at 24 hours. Inter-rater reliability of assessing qualitative hypoattenuation on NCCT was tested using an unweighted kappa. A two tailed p value < 0.05 was considered statistically significant. Statistical analysis was done using Stata IC version 12.1.

3. Results:

A total of 127 patients met study inclusion/exclusion criteria (males 53.5%; median age 68, IQR=15; median NIHSS 14, IQR=9). The median stroke symptom onset to MRI time was 158 minutes (IQR=94). On baseline MRI, all patients had positive DWI lesions. The MRI DWI-FLAIR mismatch was seen in 85/127 (67%), while NCCT hypoattenuation was seen in 111/127 (87%).

Clinical and imaging characteristics in the study sample are summarized in Table 1. Compared to the no mismatch group, patients who had mismatch on MRI DWI-FLAIR were older (median age 69.9 vs. 62.8 years, p=0.001) and had shorter median onset to MRI time (145.5 vs. 192 minutes, p=0.0003). Median rFLAIR in the mismatch and no mismatch group were 1.04 (IQR=0.06) and 1.21 (IQR=0.10) respectively (p<0.001), while the median rCT in these groups were 0.91 (IQR=0.08) and 0.8 (IQR=0.08) respectively (p<0.001). We also compared qualitative assessment of hypoattenuation on NCCT with qualitative DWI FLAIR

mismatch. 91.7% of patients in group I (normal looking NCCT) vs. 0% of patients in group IV (subacute looking infarct on NCCT) had MRI DWI-FLAIR mismatch ($p<0.001$, figure 2).

Table 1: Clinical and imaging characteristics in patients with and without MRI DWI-FLAIR mismatch.

	No mismatch (n=42)	Mismatch (n=85)	P value
Age (Median, IQR)	62.8 (12.4)	69.9 (9.9)	0.001
Sex (M, %)	61.9	49.4	0.193
Median onset to MRI time (mins)	192 (162)	145.5 (82)	0.001
Median NIHSS	12.5 (10)	14 (9)	0.122
Median NCCT ASPECTS	8 (4)	7.5 (2)	0.492
PH 1 & 2 (%)	7.5	20.7	0.073
Any ICH (%)	59.5	57.6	1.000
Endovascular therapy (%)	71.4	72.9	1.000
rFLAIR* (Median, IQR)	1.21 (0.10)	1.04 (0.06)	0.000
rCT# (Median, IQR)	0.80 (0.10)	0.91 (0.08)	0.000

IQR, Inter-quartile range; MR, Magnetic Resonance Imaging; NIHSS, National Institute of Health Stroke Scale; NCCT, non-contrast CT; PH, Parenchymal hemorrhage; ICH, Intracerebral hemorrhage; *rFLAIR, ratio of ipsilateral/contralateral FLAIR signal intensity; #rCT, ratio of ipsilateral/contralateral NCCT HU density within the circular mirror ROIs.

A statistically significant negative correlation was noted between rFLAIR and rCT (Spearman's correlation coefficient $r = -0.63$, $p<0.001$). This implied that increasing FLAIR signal intensity on the ipsilesional side is associated with a corresponding decrease in NCCT attenuation (HU) (figure 3). Similarly, a statistically significant negative correlation was noted between rCT and stroke symptom onset to MRI time (Spearman's correlation coefficient $r = -0.33$, $p<0.001$). This implied that increasing stroke onset to MRI time was associated with a corresponding decrease in NCCT attenuation (HU). This compared well to a similar statistically significant correlation between rFLAIR and stroke symptom onset to MRI time (Spearman's correlation coefficient $r = 0.27$, $p<0.001$).

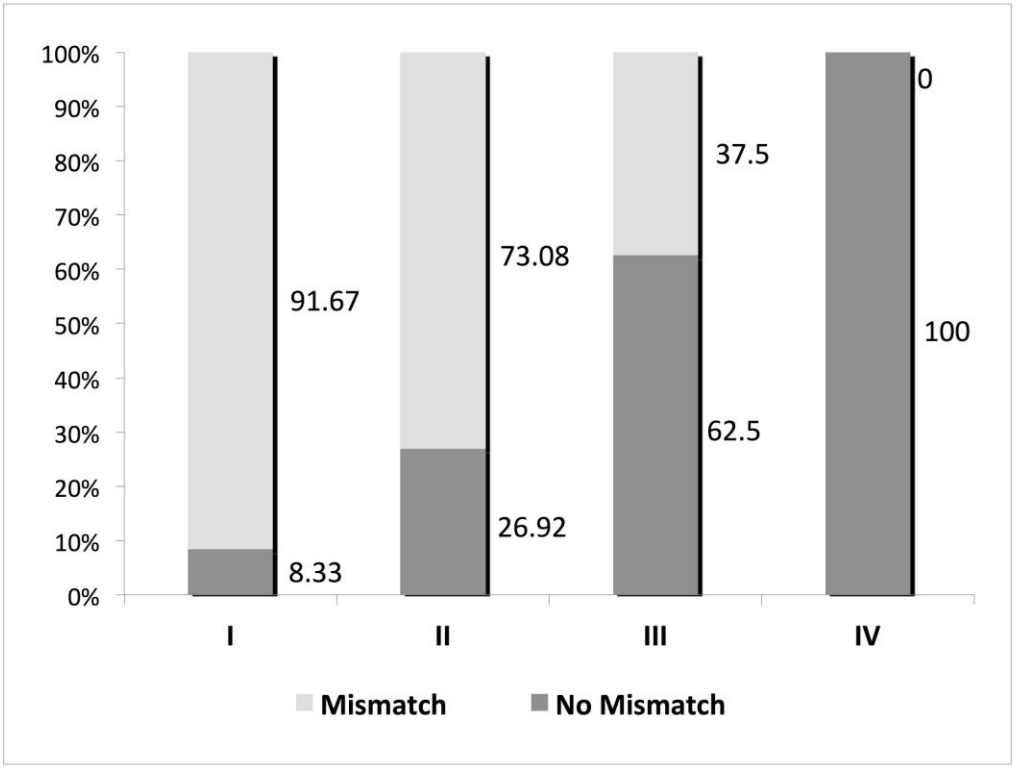

Figure 2: Qualitative assessment of NCCT attenuation (I- normal looking scans, II- slightly hypodense, III- hypodense and IV- extremely hypodense, subacute looking infarct) in comparison to presence or absence of MRI DWI-FLAIR mismatch. Y-axis describes percentage of patients with DWI- FLAIR mismatch (dark shade) in each CT hypoattenuation group.

Using ROC analyses, a rCT > 0.87 best predicted the presence of DWI-FLAIR mismatch [c statistic = 0.84 (95% CI 0.77-0.91), Sensitivity 73.75% (95%CI 62.71%-82.95%); Specificity 76.92% (95%CI 60.67-88.87%)]. A rCT > 0.9 predicted mismatch with high degree of specificity (95%,CI: 82.7-99.4%). Among patients presenting <= 4.5 hours from stroke symptom onset, 73.83% had mismatch on MRI DWI-FLAIR compared to 30% amongst those who presented > 4.5 hours ($p<0.001$). Using a rCT threshold >0.87, 63.3% of patients presenting <= 4.5 hours from stroke symptom onset did not have hypoattenuation on NCCT compared to 35% of patients who presented at >4.5 hours ($p=0.025$).

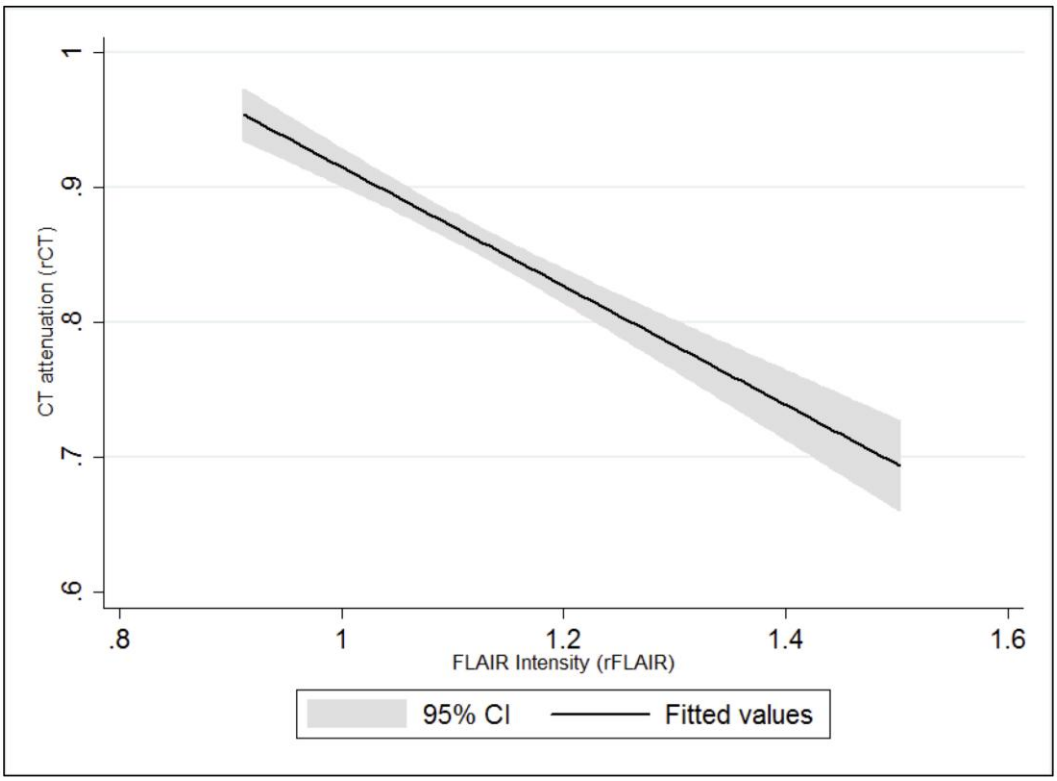

Figure 3: Relationship between rFLAIR and rCT. With increasing rFLAIR, there is a corresponding decrease in rCT in a linear fashion. Shaded area represents 95% CI. Finally, in ability to discriminate parenchymal hemorrhage at 24 hours, a model with rCT > 0.87 (yes/no) as predictor variable (c statistic = 0.6, 95% CI 0.51-0.7) was similar to the model with MRI DWI-FLAIR mismatch (c statistic = 0.6, 95% CI 0.5-0.71) (p=0.92). Similarly, a model with qualitative CT hypoattenuation dichotomized as normal to slightly hypodense (groups I and II) vs. hypodense to subacute looking (groups III and IV) (c statistic = 0.56, 95% CI 0.44–0.68) was similar to the model with MRI DWI-FLAIR mismatch in ability to discriminate parenchymal hemorhhage at 24 hours (p=0.5). Inter-rater reliability for the dichotomized CT hypoattenuation (groups I/II vs. III/IV) is high (n=40; kappa=0.88).

4. Discussion:

This study shows that qualitative and quantitative assessment of hypoattenuation on NCCT identifies the same group of patients with acute ischemic stroke as the MRI DWI-FLAIR mismatch imaging paradigm. Patients with subtle or no hypoattenuation on NCCT detected quantitavely (rCT>0.87) or qualitatively (hypoattenuation within early ischemic regions similar or less than contralateral normal white matter) are likely the same patients with DWI-FLAIR mismatch on MRI. Like the DWI-FLAIR

mismatch imaging paradigm, the degree of hypoattenuation on NCCT is a reliable bio-marker of time from stroke symptom onset and has similar ability in discriminating risk of parenchymal hemorrhage at 24 hours in patients with acute ischemic stroke.

The recent endovascular trials have shown the utility of thrombectomy in patients with acute ischemic stroke and proximal occlusions potentially up to 12 hours from stroke symptom onset (20-24). Imaging selection likely played a major role in the success of these trials, potentially even identifying patients presenting late or with wake up stroke symptoms likely to benefit from reperfusion (25). Clinical trials (DAWN, WAKE-UP, MR WITNESS) using imaging paradigms like MRI DWI-FLAIR mismatch or CT Perfusion are ongoing to show benefit of thrombectomy or thrombolysis in the late time windows. Reperfusion into brain tissue that is severely ischemic and exposed to ischemia for a long duration of time increases risk of major hemorrhage. This is likely due to progressively increasing endothelial damage and consequent blood brain barrier dysfunction over time resulting in extravasation of blood from leaky microvessels (26). The CT Perfusion imaging paradigm measures severity but does not measure duration of ischemia (27). The MRI DWI-FLAIR mismatch is potentially capable of detecting both (7). MRI, however, is not available round the clock in many centres; patients also need to be screened for metallic implants, thus prolonging time to treatment (14, 28). This study shows that hypoattenuation on NCCT is another way of identifying patients who could potentially benefit from reperfusion. Since NCCT is a quick, easily available imaging tool, it could be used instead of MRI in clinical trials testing benefit of thrombectomy or thrombolysis in patients with wake up strokes or presenting late.

A disadvantage of NCCT when detecting early ischemic changes is its modest reliability in the early presenters and in non-experts (29). This study however shows that by reliably discriminating between subtle and significant hypoattenuation, a systematic

assessment of NCCT provides a similar imaging biomarker of ischemia severity and ischemia time as MRI DWI-FLAIR mismatch. Automated quantitative assessments of hypoattenuation on NCCT have the potential of further improving reliability of NCCT for this purpose (30).

Although similar in ability to discriminate risk of hemorrhage, MRI DWI-FLAIR mismatch and NCCT hypoattenuation were only modest predictors of this risk in this study. This is understandable given that our ability to predict hemorrhage risk, even with the best of statistical models and large samples, is still modest (31-33). It is therefore important to underline the fact that MRI DWI-FLAIR mismatch and CT hypoattenuation imaging paradigms have to be tested within clinical trials before they can be shown to be of use in selecting the right patient for reperfusion therapies.

DWI-FLAIR mismatch was defined by the presence of FLAIR signal in <50% of the DWI lesion. While some previous studies have defined DWI FLAIR mismatch as absence of any FLAIR signal within the DWI lesion, only 4/127 patients would have fit that definition (7-9). This is despite many patients presenting within 3 hours of stroke symptom onset. Of note, the above are qualitative definitions. In this study, a detailed quantitative analysis by measuring FLAIR signals within the DWI lesion (rFLAIR) was performed and it demonstrated that the degree of hypoattenuation on NCCT gives the same information as MR FLAIR signal change. The small sample size and single centre nature of this study are potential limitations. This study needs to be replicated using data from larger studies. Nonetheless, we are able to demonstrate that NCCT can be used in place of MRI DWI-FLAIR mismatch in clinical trials selecting patients with wake up stroke or presenting late.

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