PAPER

Clinical and imaging predictors of intracerebral haemorrhage in stroke patients treated with intravenous tissue plasminogen activator

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Objective: To evaluate clinical, biological, and pretreatment imaging variables for predictors of tissue plasminogen activator (tPA) related intracerebral haemorrhage (ICH) in stroke patients.
Methods: 48 consecutive patients with hemispheric stroke were given intravenous tPA within seven hours of symptom onset, after computed tomography (CT) and magnetic resonance imaging (MRI) of the brain. Baseline diffusion weighted (DWI) and perfusion weighted (PWI) imaging volumes, time to peak, mean transit time, regional cerebral blood flow index, and regional cerebral blood volume were evaluated. The distribution of apparent diffusion coefficient (ADC) values was determined within each DWI lesion.
Results: The symptomatic ICH rate was 8.3% (four of 48); the rate for any ICH was 43.8% (21 of 48). Univariate analysis showed that age, weight, history of hyperlipidaemia, baseline NIHSS score, glucose level, red blood cell count, and lacunar state on MRI were associated with ICH. However, mean 24 hour systolic blood pressure and a hyperdense artery sign on pretreatment CT were the only independent predictors of ICH. Patients with a hyperdense artery sign had larger pretreatment PWI and DWI lesion volumes and a higher NIHSS score. Analysis of the distribution of ADC values within DWI lesions showed that a greater percentage of pixels had lower ADCs ($<400\times10^{-6}$ mm^2/s) in patients who experienced ICH than in those who did not.
Conclusion: Key clinical and biological variables, pretreatment CT signs, and MRI indices are associated with tPA related intracerebral haemorrhage.

Haemorrhagic transformation of a brain infarct is a major concern in acute stroke treatment. Spontaneous bleeding within the infarcted brain tissue is common, especially during the first week of ischaemic stroke.[1–4] The frequency of haemorrhagic transformation is increased in stroke patients treated with anticoagulant therapy or thrombolysis.[5–7] Symptomatic intracerebral haemorrhage (ICH) is obviously the most feared complication of thrombolysis for stroke. Different clinical and radiological factors contributing to tissue plasminogen activator (tPA) related ICH have been reported previously, such as increasing age, severe neurological deficit on admission, and the importance of the extent of parenchymal hypoattenuation on baseline computed tomography (CT).[5–7] The European cooperative acute stroke study (ECASS) investigators were first to suggest that the baseline CT data could be predictive of subsequent ICH.[8] In the ECASS II trial, the incidence of parenchymal haematoma type 2, which independently causes clinical deterioration, was significantly more frequent with the presence of large early hypodensity on baseline CT.[9] On the other hand, data on magnetic resonance imaging (MRI) markers of tPA related ICH remain limited.[10–13] Pretreatment assessment of thrombolytic candidates with a clinical, biological, CT, and multimodal MRI screening could identify more predictors of ICH. We present such a multiparametric evaluation of factors predicting tPA related ICH.

METHODS

Patients

Consecutive patients with symptoms of acute internal carotid artery (ICA) territory stroke were recruited for this prospective study.

Inclusion criteria were:

- time from symptom onset to tPA administration less than seven hours;
- absence of haemorrhage on brain CT;
- no contraindications to MRI or thrombolysis (including previous ICH);
- informed consent obtained from the patient or authorised representative.

Neurological deficit was assessed on admission and at days 1, 7, and 60 by a neurologist certified in the use of the National Institutes of Health stroke scale (NIHSS).[14] A significant neurological deficit (NIHSS score ⩾4) had to be present at the time of entry to the study. A modified Rankin scale (m-RS) score[15] was obtained on day 60.

Intravenous alteplase (Actilyse®, Boehringer Ingelheim, Biberach, Germany) was given according to a previously published protocol.[16] Briefly, patients received tPA in a dose of 0.8 mg/kg body wt (maximum 90 mg), 10% of which was given as a bolus in the first minute, followed by delivery of the remaining 90% as a constant infusion over 90 minutes. An increase in blood pressure to more than 185 mm Hg systolic or 110 mm Hg diastolic after initiation of tPA was treated with intravenous nicardipine or labetalol. Systolic and diastolic blood pressure were recorded each hour during the

Abbreviations: ADC, apparent diffusion coefficient; ECASS, European cooperative acute stroke study; EIC, early ischaemic changes; EPI, echo-planar imaging; ICA, internal carotid artery; ICH, intracerebral haemorrhage; NIHSS, National Institutes of Health stroke scale; tPA, tissue plasminogen activator; TTP, time to peak

first 24 hours. The study was reviewed and approved by the human research committee at our institution.

Demographic, clinical, laboratory, and imaging data for 46 variables (table 1) were recorded for each patient. The diagnostic criteria for hypertension were systolic/diastolic blood pressure ⩾140/90 mm Hg. The criteria for hyperlipidaemia were total cholesterol ⩾5.18 mmol/l (200 mg/dl), low density lipoprotein (LDL) ⩾1.60 g/l, and/or triglycerides ⩾2.26 mmol/l (200 mg/dl).

The pretreatment T2* weighted MRI sequences were reviewed for evidence of old asymptomatic microbleeds (rounded, homogeneous, hypointense lesions <5 mm in size[17]). Symmetrical hyposignal of the globus pallidus, indicative of calcification, and loss of signal in the cerebral arteries, indicative of thrombus, were reasons for exclusion. Lacunes were defined as subcortical infarcts 3 to 20 mm in size on T2* weighted MRI sequences.[18] The presence of leukoaraiosis on T2* weighted MRI sequences was assessed using the Fazekas rating scale.[19]

The TOAST (trial of Org 10172 in acute stroke) criteria were used to classify stroke aetiology.[20]

CT imaging and analyses

All patients underwent non-contrast CT (with a fourth generation CT scanner) before treatment. Five millimetre thick contiguous slices were produced over the whole intracranial cavity. A second scan was done at (mean (SD)) 24 (6) hours, and a third scan on day 7; a control scan was obtained at any time when neurological deterioration was observed.

The study neuroradiologist (MH), blinded to the clinical data and the results of previous or subsequent CT imaging, evaluated each scan. ICH was defined according to the National Institute of Neurological Disorders and Stroke (NINDS) tPA stroke study and the ECASS-II criteria.[5 7] Symptomatic ICH was defined as CT documented haemorrhage that was temporally related to neurological deterioration. Neurological deterioration was defined according to the PROACT II (prolyse in acute cerebral thromboembolism) criteria: at least a four point worsening on the NIHSS or a one point worsening on the NIHSS level of consciousness (item 1a), compared with the previous examination.[21]

All scans were examined for lacunes, the hyperdense artery sign, and early ischaemic changes (EIC). The volume of EIC was assessed prospectively (for example, >33% of the MCA territory), as for ECASS.[7] The hyperdense artery sign was defined as an area of increased attenuation, compared with the contralateral side of the brain, along the course of a cerebral artery, which was not consistent with atheromatous vessel wall calcification.

Table 1 Demographic, clinical, laboratory, CT, and MRI variables

Demographic and clinical variables	CT/MRI indices
Age	Lacunes
Sex	Leukoaraiosis
Weight	Early ischaemic changes
NIHSS score	Hyperdense artery sign
Systolic blood pressure	DWI lesion volume
Diastolic blood pressure	Mean ADC
Mean 24-hour SBP	PWI lesion volume
Mean 24-hour DBP	TTP
Hypertension on admission	RMTT
Glucose	rrCBV
Cholesterol	rCBFi
C reactive protein	Microbleeds
White blood cell count	Presence of arterial occlusion
Red blood cell count	Site of occlusion
Platelet count	Recanalisation
Packed cell volume	Aetiology of stroke
International normalised ratio	
Cardioembolic source	
Partial thromboplastin time	
Fibrinogen	
Treatment delay	
Cigarette smoking	
Alcohol abuse	
Hypertension	
Diabetes	
Hyperlipidaemia	
Coronary artery disease	
Peripheral vascular disease	
Cerebrovascular diseases	
Current use of antiplatelets	

ADC, apparent diffusion coefficient; CT, computed tomography; DBP, diastolic blood pressure; DWI, diffusion weighted imaging; MRI, magnetic resonance imaging; PWI, perfusion weighted imaging; RMTT, regional mean transit time; rCBFI, relative cerebral blood flow index; rrCBV, relative regional cerebral blood volume; SBP, systolic blood pressure; TTP, time to peak.

MRI methods

MRI was done at presentation and on day 1 after stroke onset using a 1.5 T whole body MR imager (Siemens AG, Erlangen, Germany), equipped with enhanced gradient hardware for echo-planar imaging (EPI). MRI protocol parameters have already been published.[22] Sequences were always done in the same order: (1) time of flight turbo magnetic resonance angiography; (2) T2* weighted gradient echo (GE) sequence; (3) EPI isotropic diffusion weighted imaging (DWI); (4) perfusion weighted MRI (PWI) performed with GE EPI, using bolus passage of contrast agent.

Data collection

Various MRI indices—including baseline DWI and PWI lesion volumes—were determined by a senior neuroradiologist who was unaware of the clinical data. DWI and PWI indices were measured by placing regions of interest (ROI) within the DWI and PWI lesions manually.

To define DWI lesion volume, we used the trace images obtained at the highest b value ($b = 1000$ s/mm^2). The global lesion volume was determined by multiplying the area of diffusion hyperintensity by the sum of the slice thickness and the interslice gap thickness. Apparent diffusion coefficient (ADC) maps were generated by software using three values of b ($b = 50$, $b = 500$, and $b = 1000$ s/mm^2). Pixel-by-pixel ADC values within each DWI lesion were grouped into 11 distinct classes ($<250\times10^{-6}$ mm^2/s to $>1150\times10^{-6}$ mm^2/s). The percentage of pixels within each class was determined. The mean lesional ADC value was calculated for each patient.

Perfusion maps were generated from the concentration–time curve. A gamma variate fit was used on a pixel-by-pixel basis to compute parameter images for absolute time-to-peak (TTP) of signal drop.[22] The PWI lesion volume was measured on the TTP maps (manual contouring). The global PWI lesion volume was determined by multiplying the area of perfusion abnormality by the sum of the slice thickness and the interslice gap thickness.

The evaluation of haemodynamic status also included relative regional cerebral blood volume (rrCBV), assessed as the area under the concentration–time curve, relative mean transit time (rMTT), assessed as the first moment of the concentration–time curve, and regional cerebral blood flow index (rCBFi), assessed as the ratio rrCBV to rMTT within the perfusion deficit and the normal appearing contralateral mirror area.[23]

Vessel occlusions were categorised on magnetic resonance angiography (MRA) as proximal (ICA and M1 segment of the middle cerebral artery (MCA)) or distal (M2 segment of the MCA, distal branches of the MCA, and anterior cerebral

artery (ACA)). Recanalisation was assessed on day 1 MRA (no recanalisation versus partial or full recanalisation).

Reproducibility measurement

For the DWI and PWI lesion volume measurements, two experienced observers measured the lesion on two occasions and the mean value was used. The interobserver and intraobserver variation in measurements was assessed by comparing the differences in measurements for the 48 cases. The intraobserver and interobserver reliability (r) was $r = 0.95$, with a mean deviation of less than 5% for intraobserver reproducibility. The intraobserver and interobserver reliabilities for lacune, leukoaraiosis, and microbleed detection on T2* sequences were $r = 0.80$, 0.80, and 0.90, respectively. The intraobserver and interobserver reliability for the hyperdense artery sign detection on baseline CT scan was $r = 0.85$.

Statistical methods

Quantitative data are expressed as mean (SD). We used Fisher's exact test to compare two binary variables and Pearson's χ^2 test to compare two categorical variables in order to assess the significance of the association of pairs of non-continuous variables. We applied the linear by linear association test for two ordinal variables. Spearman's rank order correlation coefficient was calculated for pairs of ordinal, continuous, and mixed (one ordinal and one continuous) variables. We applied the two sample t test for one continuous variable and a binary factor (two groups). Multivariable analysis of the predictors of ICH was undertaken using a logistic regression model. The criterion for selecting explanatory variables was liberal ($p<0.20$). Differences were considered statistically significant at $p<0.05$. SPSS 10.0 (SPSS Inc, Chicago, Illinois, USA) was used for all calculations.

RESULTS

Between March 2001 and October 2002, MRI was undertaken in 94 consecutive ischaemic stroke patients admitted to our stroke unit. This represents 19% of patients admitted to hospital during the same period. Forty eight of these 94 patients (25 men and 23 women) underwent MRI before tPA. Their mean (SD) age was 63.8 (13.6) years. The mean NIHSS score was 13.7 (5.8). Time from stroke onset to CT was 2.68 (1.13) hours; time from stroke onset to MRI was 3.52 (1.27) hours. Time from stroke to tPA was 4.35 (1.20) hours.

Twenty patients (41.7%) had a hyperdense artery sign on baseline CT: dense ICA sign in seven patients, dense MCA sign in 12 patients, and dense insular artery sign in three patients. Pretreatment MRA showed vessel occlusion in 46 patients, as follows: ICA+M1 MCA in 11; M1 MCA in 18; M2 and distal branches of the MCA in 15; ACA in two. Mean pretreatment DWI lesion volume was 47.5 (59.3) cm^3; mean PWI lesion volume was 110.9 (56.8) cm^3; mean ADC was 772.9 (129.3)$\times 10^{-6}$ mm^2/s.

The rate for symptomatic haemorrhage was 8.3% (four of 48). None of these four patients died. The rate for any haemorrhage was 43.8% (21 of 48). According to the NINDS criteria, six patients had intracerebral haematomas and 15 had haemorrhagic cerebral infarcts. According to the ECASS-II criteria, six patients had parenchymal haemorrhages (PH 1 in two cases and PH 2 in four cases) and 15 had haemorrhagic infarcts (HI 1 in 12 cases and HI 2 in three cases).

No recurrent stroke was observed. Death occurred in four patients (8.3%) during a two month follow up. Stroke aetiology was classified as follows, according to the TOAST criteria: 22 patients with large vessel disease, 18 with a cardioembolic source, four with small vessel disease, and four with cryptogenic stroke.

Single explanatory variable analysis of patient characteristics, biological variables, and imaging parameters predicting ICH are presented in tables 2 and 3. Age, weight, history of hyperlipidaemia, baseline NIHSS score, admission glucose level, red blood cell count, mean 24 hour systolic blood pressure, and lacunar state on T2* were all associated with ICH.

Multivariable analysis of the predictors of ICH is presented in table 4. Mean 24 hour systolic blood pressure and a hyperdense artery sign on pretreatment CT were independent predictors of ICH. We measured the area under the receiver operating characteristic (ROC) curve to assess the prognostic power of our logistic regression model (fig 1). The model's ability to discriminate patients who experienced ICH from those who did not was excellent (area under the ROC curve = 0.82; number of observations = 48).

The correlations between clinical, CT, and MRI parameters and the hyperdense artery sign are presented in table 5. Patients with a hyperdense artery sign had larger baseline

Table 2 Single explanatory variable analysis of demographic, clinical, and biological predictors of intracerebral haemorrhage

Variables	HT group (n = 21)	Non-HT group (n = 27)	Total	p Value
Age (years)	68.9 (8.8)	59.8 (15.4)	63.8 (13.6)	**0.01**
Weight (kg)	75.5 (14.7)	64.7 (13.9)	69.6 (15.1)	**0.01**
History of hypertension (%)	66.7	44.4	54.2	0.15
History of hyperlipidaemia (%)	52.4	22.2	35.4	**0.04**
History of atheroma (%)	57.1	29.6	41.7	0.08
NIHSS score	15.5 (5.6)	12.2 (5.6)	13.7 (5.8)	**0.05**
Mean 24 hour SBP (mm Hg)	151.8 (16.0)	134.2 (18.9)	142.1 (19.5)	**0.001**
Mean 24 hour DBP (mm Hg)	81.9 (8.9)	76.7 (10.8)	79.0 (10.2)	0.08
Glucose (mmol/l)	7.8 (2.2)	6.4 (2.6)	7.0 (2.5)	**0.05**
Platelet count ($\times 10^9$/l)	225.8 (59.8)	243.3 (68.5)	235.6 (64.8)	0.36
White blood cell count ($\times 10^9$/l)	8.5 (2.4)	8.7 (2.5)	8.6 (2.4)	0.77
Red blood cell count ($\times 10^{12}$/l)	4.6 (0.4)	4.3 (0.5)	4.5 (0.5)	**0.04**
Cholesterol (mmol/l)	5.3 (1.0)	5.2 (1.0)	5.2 (1.0)	0.83
Fibrinogen (g/l)	3.6 (0.6)	3.3 (0.9)	3.5 (0.8)	0.23
Delay to tPA (min)	206 (20)	272 (18)	261 (72)	0.24

Values are mean (SD) unless indicated otherwise. Significant values in bold.
DBP, diastolic blood pressure; HT, haemorrhagic transformation; NIHSS, National Institutes of Health stroke scale; SBP, systolic blood pressure; tPA, tissue plasminogen activator.

Table 3 Single explanatory variable analysis of CT and MRI predictors of intracerebral haemorrhage

Variables	HT group (n = 21)	Non-HT group (n = 27)	Total	p Value
EIC (%)	76.2	63	68.8	0.37
EIC>1/3 MCA territory (%)	19	3.7	10.4	0.15
Hyperdense artery sign (%)	57.1	29.6	41.7	0.08
DWI lesion volume (cm^3)	58.3 (65.0)	39.0 (54.2)	47.5 (59.3)	0.28
ADC ($\times 10^{-6}$ mm^2/s)	760.2 (142.2)	783.2 (119.7)	772.9 (129.3)	0.55
PWI volume (cm^3)	123.6 (48.4)	102 (61.4)	110.9 (56.8)	0.19
TTP (s)	25.6 (7.1)	24.6 (4.5)	25.0 (5.7)	0.55
rMTT (s)	14.4 (4.7)	14.4 (2.8)	14.4 (3.7)	0.95
rCBFI	4.5 (2.5)	5.6 (2.4)	5.1 (2.5)	0.14
rrCBV	33.4 (13.7)	38.2 (11.7)	36.1 (12.7)	0.20
Lacunes on T2* (%)	57.1	22.2	37.5	**0.02**
MB on T2* (%)	33.3	11.1	20.9	0.08
Recanalisation day 1 MRA (%)	50	55.6	52.1	0.32

Values are mean (SD) unless indicated otherwise.
ADC, apparent diffusion coefficient; CT, computed tomography; DWI, diffusion weighted imaging; EIC, early ischaemic changes; HT, haemorrhagic transformation; MB, microbleeds; MCA, middle cerebral artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PWI, perfusion weighted imaging; rCBFI, relative cerebral blood flow index; rMTT, regional mean transit time; rrCBV, relative regional cerebral blood volume; TTP, time to peak.

PWI and DWI lesion volumes, a more severe initial neurological deficit, and a worse outcome.

The frequency distribution of ADC values within pretreatment DWI lesions is presented in fig 2. A greater percentage of pixels had lower ADCs ($<400\times10^{-6}$ mm^2/s) in patients who experienced ICH than in patients who did not.

DISCUSSION

Multimodal MRI has the potential to select patients with evidence of salvageable brain tissue beyond the three hour time window.[24] However, although meta-analyses of tPA given within the three to six hour time window shows that it has some efficacy, the benefit is smaller and the risk of bleeding is greater than in the optimal three hour time window.[25] Thus the identification of predictors of ICH may improve patient selection and could lead to the safer use of thrombolysis beyond three hours.

Recent studies suggest that diffusion weighted MRI can help to identify patients at increased risk of ICH.[10–12] Our study represents the largest series so far in which ADC was calculated for each pixel in the whole ischaemic area to determine the influence of ADC values on the risk of ICH. We observed a significant influence of pretreatment ADC values on the bleeding risk. A greater percentage of pixels had lower ADCs ($<400\times10^{-6}$ mm^2/s) in patients who experienced ICH than in patients who did not. Tong *et al* had already shown that ischaemic lesions destined to result in haemorrhagic transformation (HT) had lower ADC values than non-HT destined regions.[10] Selim *et al* have also shown that the absolute volume of ischaemic tissue with ADC values below a cut off of 550×10^{-6} mm^2/s was associated with haemorrhagic transformation after tPA.[12] Our results are consistent with these findings, with a lower cut off value. Careful analysis of the pretreatment ADC values could be helpful for identifying patients at increased risk of ICH. However, the feasibility of pretreatment ADC analysis should be examined prospectively in future studies. Additional MRI evaluation of blood–brain barrier disruption is also needed for a better assessment of the ischaemic damage to brain microvessels that contributes to the risk of haemorrhagic transformation after late thrombolysis with tPA.[26] We were unable to detect any significant influence of the baseline DWI and PWI lesion volumes, TTP, rMTT, rCBFi, or rrCBV on the risk of ICH.

One limitation of our study is the use of relative haemodynamic indices. Accordingly, absolute quantification of CBF is needed before treatment to determine the haemodynamic threshold for risk of haemorrhagic transformation. Ueda *et al* have assessed cerebral blood flow in the territory of occluded vessels by single photon emission computed tomography (SPECT) in 20 stroke patients who underwent intra-arterial thrombolysis.[27] Residual blood flow was significantly lower in the five patients who experienced ICH than in the 15 who did not.

The multivariable analyses in our study showed that the presence of a hyperdense artery sign on pretreatment CT was an independent predictor of ICH. The hyperdense middle cerebral artery sign is a well known predictor of occlusion of that artery with subsequent development of a large infarct and with a poor clinical outcome, even when patients are given tPA within three hours.[28 29] In our series, patients with a hyperdense artery sign had a more severe neurological deficit, a worse clinical outcome, and a specific pretreatment MRI pattern with larger DWI and PWI lesion volumes. The vast majority of patients with internal carotid artery or middle cerebral artery occlusion have poor collateral blood flow with a subsequent low flow state and increased

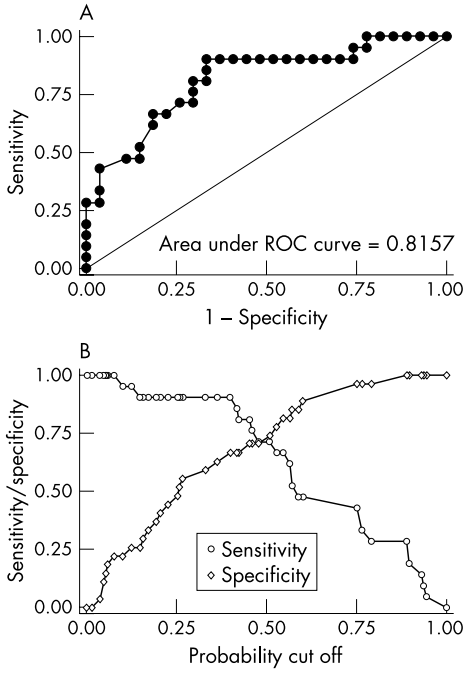

Figure 1 Receiver operating characteristic (ROC) curves assessing prognostic power of 24 hour systolic blood pressure plus a hyperdense artery sign in relation to intracerebral haemorrhage.

Table 4 Multivariate analysis of prediction of intracranial haemorrhage (n = 48)

Variable	Regression coefficient	SE	Estimated odds ratio	95% CI	p Value
Mean 24 hour SBP	0.075	0.025	1.078	1.027 to 1.131	0.003
HAS (0 = no; 1 = yes)	1.892	0.822	6.630	1.323 to 33.235	0.02
Constant	−11.772	3.783	–	–	0.002

Adjusted R^2 (Nagelkerke) = 0.42; area under the ROC curve = 0.82.
The two explanatory variables (mean 24 hour systolic blood pressure and a hyperdense artery sign) plus the constant represent the simplest adequate model.
CI, confidence interval; HAS, hyperdense artery sign; SBP, systolic blood pressure.

haemoglobin concentration, leading to an increased attenuation on CT.[30] These patients with a proximal occlusion experience an immediate fall in blood flow in the territories supplied by the lenticulostriatal arteries, where collaterals are limited, leading to an increased risk of haemorrhagic transformation where ischaemic injury is greatest.[31]

With respect to clinical variables, our data corroborate previous studies showing that increasing age is associated with an increased risk of tPA related ICH.[5–7 32] In our study, the presence of lacunes on MRI was associated with an increased risk of ICH. Only a non-significant trend towards a higher risk of bleeding was detected for patients with microbleeds on T2* sequences. Other studies have shown that elderly patients with evidence of bleeding-prone microangiopathy are at higher risk of ICH under antithrombotic therapy.[33 34] High blood pressure during the first 24 hours was an independent predictor of ICH in our study. Raised blood pressure has already been related to ICH following thrombolysis for stroke.[5 7 32] These data highlight the importance of a careful monitoring of blood pressure within the first 24 hours.

Our results are consistent with previous findings suggesting an association between baseline serum glucose and tPA related ICH.[32 35 36] There is experimental evidence that hyperglycaemia has a deleterious effect on ischaemic brain damage. In animal models, hyperglycaemia has been found to exaggerate blood–brain barrier injury, resulting in haemorrhagic transformation of the cerebral infarct.[37 38] Thrombolytics are matrix metalloproteinases that may aggravate ischaemia induced damage to the basal lamina with subsequent loss of vessel wall integrity followed by haemorrhage.[38] This deleterious effect of tPA may be potentiated in the presence of hyperglycaemia.

Table 5 Correlations between pretreatment CT, MRI, clinical variables, and hyperdense artery sign on baseline CT (Spearman's ρ)

MRI indices	Correlation coefficient	p Value
DWI lesion volume (cm^3)	0.57	**<0.0001**
ADC (10^{-6} mm^2/s)	−0.14	0.33
PWI lesion volume (cm^3)	0.51	**<0.0001**
TTP (s)	0.003	0.98
rrCBV	−0.04	0.77
RCBFI	−0.20	0.18
RMTT (s)	−0.01	0.95
EIC (%)	0.23	0.11
NIHSS score	0.56	**<0.0001**
Day 60 m-RS score	0.42	**0.004**

ADC, apparent diffusion coefficient; CT, computed tomography; DWI, diffusion weighted imaging; EIC, early ischaemic changes; MRI, magnetic resonance imaging; m-RS, modified Rankin scale; NIHSS, National Institutes of Health stroke scale; PWI, perfusion weighted imaging; rCBFI, relative cerebral blood flow index; rMTT, regional mean transit time; rrCBV, relative regional cerebral blood volume; TTP, time to peak.

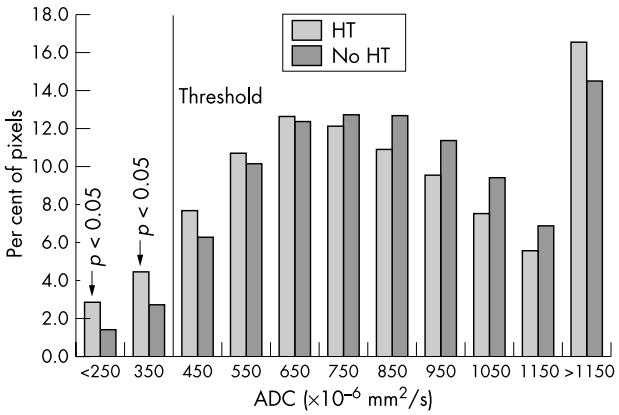

Figure 2 Frequency distribution of apparent diffusion coefficient (ADC) values within lesions identified on diffusion weighted imaging. HT, haemorrhagic transformation.

The present monocentre study has several potential limitations. Because there were only four symptomatic haemorrhages and four PH2 haematomas, we could not carry out a separate study of the factors predicting severe ICH. The spectrum of haemorrhagic transformation following tPA administration differs widely, encompassing trivial haemorrhagic petechiae and severe haematoma with a significant space occupying effect such as PH2 haematomas.[9] However, some investigators consider that the difference between symptomatic and asymptomatic haemorrhages may be related more to the degree of bleeding than to differences in pathophysiology.[31 39] More information is needed on the predictors of tPA related severe haemorrhagic transformation and will probably come from multicentre studies, as the absolute number of severe tPA related cerebral haemorrhages is small. The lack of statistical power may also have prevented us from detecting any influence of early ischaemic CT changes on the cerebral bleeding risk following tPA administration.

Conclusions

This prospective, exhaustive, and homogeneous study shows that key clinical and biological variables, pretreatment CT signs, and MRI indices are predictors of tPA related ICH. The critical combination of these different factors may strongly influence the risk of bleeding. The next step would be to validate a multiparametric model predicting tPA related ICH in a larger cohort of patients with acute ischaemic stroke.

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