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Computed Tomography Perfusion Derived Blood-Brain Barrier Permeability Does Not Yet Improve Prediction of Hemorrhagic Transformation

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Keywords

Brain · Ischemic stroke · Computed tomography · Nonlinear regression permeability · Hemorrhagic transformation · Prediction

Abstract

Introduction: Hemorrhagic transformation (HT) in acute ischemic stroke can occur as a result of reperfusion treatment. While withholding treatment may be warranted in patients with increased risk of HT, prediction of HT remains difficult. Nonlinear regression analysis can be used to estimate blood-brain barrier permeability (BBBP). The aim of this study was to identify a combination of clinical and imaging variables, including BBBP estimations, that can predict HT. ***Materials and Methods:*** From the Dutch acute stroke study, 545 patients treated with intravenous recombinant tissue plasminogen activator and/or intra-arterial treatment were selected, with available admission extended computed tomography (CT) perfusion and follow-up imaging. Patient admission treatment characteristics and CT imaging parameters regarding occlusion site, stroke severity, and BBBP were recorded. HT was assessed on day 3 follow-up imaging. The association between potential predictors and HT was analyzed using univariate and multivariate logistic regression. To compare the added value of BBBP, areas under the curve (AUCs) were created from 2 models, with and without BBBP. ***Results:*** HT occurred in 57 patients (10%). In univariate analysis, older age (OR 1.03, 95% CI 1.006–1.05), higher admission National Institutes of Health Stroke Scale (NIHSS; OR 1.13, 95% CI 1.08–1.18), higher clot burden (OR 1.28, 95% CI 1.16–1.41), poor collateral score (OR 3.49, 95% CI 1.85–6.58), larger Alberta Stroke Program Early CT Score cerebral blood volume deficit size (OR 1.26, 95% CI 1.14–1.38), and increased BBBP (OR 2.22, 95% CI 1.46–3.37) were associated with HT. In multivariate analysis with age and admission NIHSS, the addition of BBBP did not improve the AUC compared to both independent predictors alone (AUC 0.77, 95% CI 0.71–0.83). ***Conclusion:*** BBBP predicts HT but does not improve prediction with age and admission NIHSS.

Introduction

Hemorrhagic transformation (HT) is a serious complication of acute ischemic stroke. Larger parenchymal HT can cause death or severe disability, but smaller HT

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also have been related to worse outcome [1, 2]. In clinical practice, with intravenous recombinant tissue plasminogen activator (IV-rtPA) treatment given within 3 h, HT occurs in 12% of cases [3]. In some clinical trials higher incidences (up to 40%) were found, with rates depending on patient selection, time to treatment, definition of HT, and time to follow-up [4–7]. In patients treated with IV-rtPA and subsequent HT, mortality can be as high as 9% (with symptomatic HT) and morbidity up to 50% [1, 8].

Risk factors for HT have been investigated in a recent meta-analysis and include higher age and higher stroke severity [9]. Several scores can help to predict HT, but none has achieved widespread use in clinical practice [10–12]. The meta-analysis and most of these scores do not incorporate information from computed tomography (CT) angiography (CTA) and CT perfusion (CTP) imaging. Several CT imaging parameters related to the ischemic lesion have been associated with an increased risk of HT: large vessel occlusion and collateral score on CTA and infarct core volume and ischemic lesion volume on CTP [13–17].

Disturbance of the blood-brain barrier (BBB) has been implicated in HT occurrence and can be measured with CTP [18–21]. This is based on the assumption that leakage of contrast agent into the extravascular space may indicate a disrupted BBB that may more likely evolve into a HT. However, none of the papers assessing BBB permeability (BBBP) were included in the recent meta-analysis [9, 18–21]. The Patlak model is the most frequently used model to described BBBP but only considers leakage and does not take tissue perfusion into account [22]. Other methods to estimate BBBP, like non-linear regression (NLR) with a perfusion model have demonstrated to be more reliable and robust [23]. Prediction of HT may therefore also improve by using this method, as previously has been shown in a small group of patients [24].

The aim of this study was to assess the added value of BBBP estimations to known clinical and imaging variables that predict the risk of HT.

Methods

Study Design

Patients were included from the prospective multicenter Dutch acute stroke study (DUST), which aims to assess the additional value of CTP and CTA in predicting outcome of acute ischemic stroke patients [25, 26]. Adult patients were included with a clinical diagnosis of acute ischemic stroke, with a National Institutes of Health Stroke Scale (NIHSS) of ≥2, or 1 if an indication for IV-rtPA was present [25, 26]. This study was approved by the local institutional ethical review boards of the participating centers. All patients or family gave signed informed consent, unless a patient died before consent could be obtained. In that case, the medical ethics committee waived the need for consent [25, 26].

Patient Selection

From the DUST study database, with patient inclusion between May 2009 and August 2013, we selected all patients treated with IV-rtPA and/or intra-arterial treatment (thrombolysis or mechanical thrombectomy), a good quality extended CTP (meaning a total acquisition time of 210 s or more) on admission and available follow-up imaging. We collected clinical data on age, sex, history of stroke, diabetes, atrial fibrillation, myocardial infarction, or hypertension, admission NIHSS, treatment with IV-rtPA, and/or intra-arterial treatment. The inclusion process is clarified in the flow chart (Fig. 1).

Image Protocol

All patients underwent non-contrast CT (NCCT) and CTP of the brain and CTA of the cervical and cerebral vessels on admission. Follow-up NCCT (in small minority MRI) was done at 3 days (±2 days) or earlier in case of clinical deterioration. Reasons for no follow-up imaging were as follows: no permission for follow-up, or poor condition of the patient, or very rapid recovery and discharge within 24 h before follow-up could be done. Scan protocols and parameters have been described in detail previously [25, 26].

Image Analysis

All imaging data were evaluated by 1 of 3 observers (I.C. van der Schaaf, B.K.V., and J.W.D), all with at least 5 years of experience in stroke imaging. Only the side of symptoms was provided for the evaluation.

Non-Contrast CT

On the follow-up scan, HT was classified according to the radiological ECASS criteria only, because HT-related symptomatology was not rigorously collected [27].

CT Perfusion

Cerebral blood volume (CBV), cerebral blood flow, mean transit time, and time to peak in the whole brain were automatically calculated from CTP data utilizing commercially available CTP software (Extended Brilliance Workstation 4.5, Philips Healthcare). Presence of a perfusion deficit on admission was defined as a focal asymmetry on the mean transit time, cerebral blood flow, or CBV map matching a part or the whole of the middle cerebral artery flow territory. The infarct core was evaluated on CBV maps and classified with Alberta Stroke Program Early CT Score (ASPECTS) [28].

A model based method to estimate permeability by fitting a mathematical tissue response model using NLR to describe the attenuation curves obtained from the extended acquisition was used to estimate the BBBP surface area product (PS) [23]. Voxels within the skull, that had a CT value >17 or <55 HU and a CBV <9 mL/100 g, were classified as brain tissue and included in the analysis. A symmetry plane was manually aligned to the midsagittal plane in order to separate the hemispheres. Prior to the nonlinear regression procedure a 3D time intensity profile similarity bilateral filtering was applied. Permeability surface area was calculated relative to the average in the non-affected hemisphere [23]. This measurement is referred to as BBBP in this study.

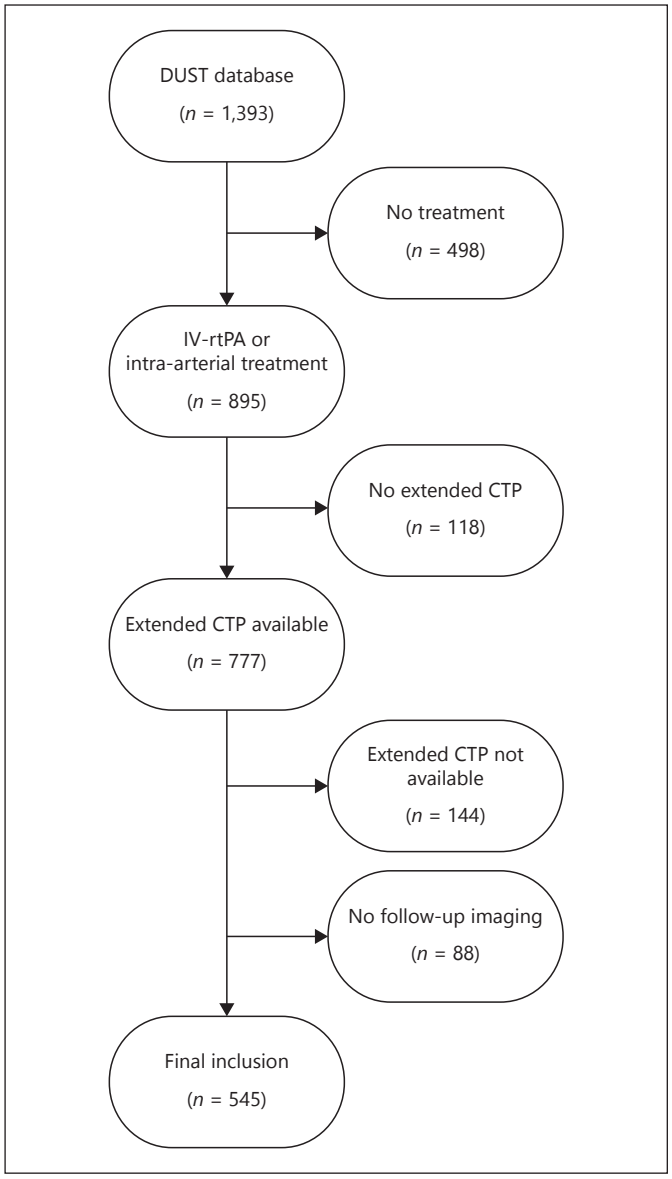

Fig. 1. Inclusion flow chart.

CT Angiography

Admission CTA provided data on clot burden score and collateral score. These scoring systems have been described in detail previously [14, 29, 30].

Statistical Analysis

Patient characteristics and imaging data were presented as numbers with percentages, means with SD or medians with IQR. Missing values occurred in some variables and were substituted with single imputation. The association between variables and HT was analyzed using univariate and multivariate logistic regression analysis. Because we had only a limited number of outcomes, only 6 variables could be selected maximally to have at least 10 outcomes per variable. All selected variables are known predictors of HT found in literature [9]. Variables analyzed were age (per year), admission NIHSS (per point), clot burden score (0–10), collateral score (good or poor), decreased CBV (ASPECTS 0–10), and NLR BBBP values. All these 6 variables were used in univariate and multivariate logistic regression analysis. Receiver operating curves (ROCs) were made of a model with and without BBBP and the areas under the curve (AUCs) were determined. Statistical computations were carried out using SPSS 23.0 (IBM Corporation, NY, USA).

Results

From the 1393 patients included in the DUST study, 895 (64.2%) received IV-rtPA or intra-arterial treatment (Fig. 1). Of these, 777 had an extended CTP and this could be assessed in 633 cases. The main reason for excluding extended CTP scans was the sensitivity of the BBBP measurement pre- and post-processing techniques for patient movements. In the final inclusion remained 545 patients who also had available follow-up imaging (CT 92% and MRI 8%). On follow-up, HT was found in 57 cases (10%). ECASS types were as follows: 12 HI (21%), 17 HI-2 (30%), 15 PH-1 (26%), and 13 PH-2 (23%; Table 1). The percentage HT in all patients with follow-up imaging in the DUST study was comparable (11%) to the percentage found in the population of this study.

In univariate analysis (Table 2) older age, higher NIHSS, higher clot burden, poor collateral score, larger ASPECTS CBV deficit size, and increased BBBP were all associated with HT. In a multivariate analysis with all selected variables remaining in the model, only age and NIHSS were independent predictors of HT (AUC 0.77, 95% CI 0.71–0.83). The ROC curves of the model with and without BBBP are shown in Figure 2. The addition of BBBP as a variable did not change the AUC (0.77, 95% CI 0.71–0.83) of the model.

In additional univariate analysis, the relation between BBBP and PH-2 type HT was not significant (but based on only 13 outcomes). In a sub-analysis of patients with a proven intracranial arterial occlusion on admission CTA ($n = 299$), BBBP was neither significantly associated with PH-2 type HT in univariate analysis, nor did it add to prediction of all types of HT with age and admission NIHSS in multivariate analysis.

Discussion

The main finding of this study is that BBBP estimated by means of nonlinear regression can predict HT in acute ischemic stroke. However, BBBP has no additional pre-

Table 1. Clinical and imaging characteristics

	All patients (n = 545)	HT patients (n = 57)	No HT patients (n = 488)	p value
Clinical parameters				
Age, years, median (IQR)	68 (58–77)	71 (65–81)	67 (57–76)	0.01*
Gender, female, n (%)	214 (39)	22 (39)	192 (39)	0.91
History of stroke, n (%)	122 (22)	16 (28)	106 (22)	0.28
History of diabetes, n (%)	73 (13)	7 (12)	66 (14)	0.79
History of atrial fibrillation, n (%)	56 (10)	10 (18)	46 (9)	0.56
History of myocardial infarction, n (%)	68 (13)	9 (16)	59 (12)	0.42
History of hypertension, n (%)	280 (51)	34 (60)	246 (50)	0.19
NIHSS, median (IQR)	8 (4–13)	13 (9–19)	7 (4–12)	0.0001*
IAT and/or MT, n (%)	44 (8)	9 (16)	35 (7)	0.02*
Imaging parameters				
Time to scan, min, median (IQR)	89 (64–135)	85 (58–135)	90 (65–135)	0.19
Admission CTA				
Clot burden score (0–10), median (IQR)	10 (8–10)	8 (5–10)	10 (8–10)	0.0001*
Poor collateral score, n (%)	70 (13)	17 (30)	53 (11)	0.00005*
Admission CTP				
Size CBV deficit, ASPECTS, median (IQR)	10 (8–10)	8 (5–10)	10 (8–10)	0.0001*
NLR permeability ratio (BBBP), median (IQR)	1.07 (0.96–1.29)	1.31 (1.01–1.60)	1.06 (0.95–1.26)	0.001*
Follow-up NCCT, n (%)				
All HT	57 (10)	57 (100)	N/A	N/A
PH-2	13 (2)	13 (23)	N/A	N/A

χ^2 test was used to compare categorical variables and Mann-Whitney U test for continuous variables.
* All $p < 0.05$.

ASPECTS, Alberta Stroke Program Early CT Score; BBBP, blood-brain barrier permeability; CBV, cerebral blood volume; CT, computed tomography; CTA, CT angiography; CTP, CT perfusion; HT, hemorrhagic transformation; IAT, intra-arterial thrombolysis; IV-rtPA, intravenous recombinant tissue plasminogen activator; NCCT, non-contrast CT; NIHSS, National Institutes of Health Stroke Scale; NLR, nonlinear regression; MT, mechanical thrombectomy; PH, parenchymal hemorrhage.

Table 2. Univariate and multivariate analysis for BBBP and other predictors of HT in patients treated with IV-rtPA or intra-arterial treatment (n = 545)

	Univariate		Multivariate without BBBP		Multivariate with BBBP	
	OR	95% CI	OR	95% CI	OR	95% CI
Clinical parameters						
Age, per year	1.03	1.006–1.05*	1.03	1.003–1.05*	1.03	1.002–1.05*
NIHSS, per point	1.13	1.08–1.18*	1.09	1.04–1.15*	1.09	1.04–1.15*
Clot burden score (0–10)	1.28	1.16–1.41*	1.10	0.94–1.27	1.09	0.93–1.27
Poor collateral score	3.49	1.85–6.58*	1.32	0.62–2.81	1.30	0.61–2.78
Size CBV deficit, ASPECTS	1.26	1.14–1.38*	1.04	0.90–1.20	1.03	0.88–1.19
NLR permeability ratio (BBBP)	2.22	1.46–3.37*	N/A	N/A	1.20	0.72–2.02

χ^2 test was used to compare categorical variables and Mann-Whitney U test for continuous variables.
* All $p < 0.05$.

ASPECTS, Alberta Stroke Program Early CT Score; BBBP, blood-brain barrier permeability; CBV, cerebral blood volume; CT, computed tomography; CTA, CT angiography; CTP, CT perfusion; HT, hemorrhagic transformation; IAT, intra-arterial thrombolysis; IV-rtPA, intravenous recombinant tissue plasminogen activator; NCCT, non-contrast CT; NIHSS, National Institutes of Health Stroke Scale; NLR, nonlinear regression; MT, mechanical thrombectomy; PH, parenchymal hemorrhage.

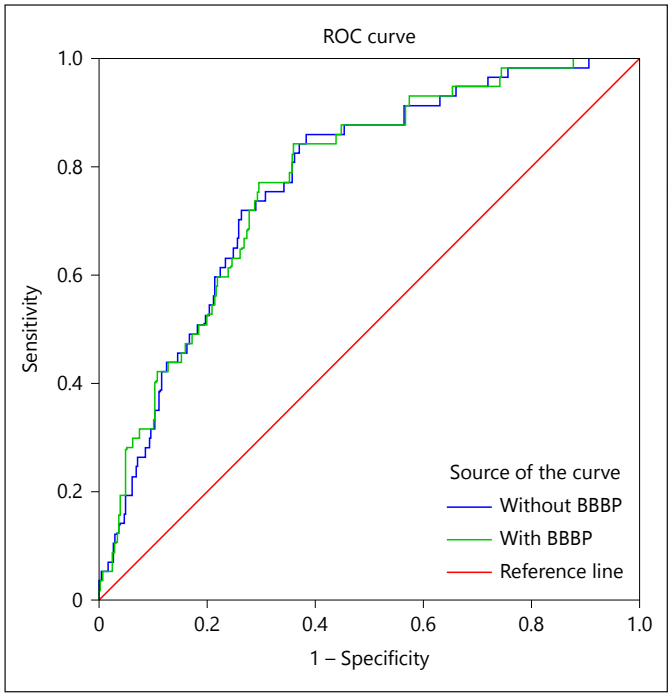

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Fig. 2. ROC of model with and without BBBP. ROC, receiver operating curves; BBBP, blood-brain barrier permeability.

dictive value in combination with other predictors, like age and admission NIHSS.

The maximum AUC for predicting HT found in our study was relatively low at 0.77, but was within the range of the results of other multivariate analyses in studies investigating predictors of HT with CTP (range 0.69–0.92) [13, 16, 17, 19, 31]. We did find a significant relation between CBV deficit and BBBP, and the occurrence of HT in univariate analysis, but this could not be confirmed in our multivariate analysis. We chose not to use admission NCCT variables in our study because the number of variables we could use was limited by the number of outcomes.

Several papers also describe a predictive value of BBBP measurements [19–21, 32, 33]. The acquisition and post-processing techniques of assessing BBBP is different in all papers, which makes direct comparison difficult. Although all these studies showed a positive association between BBBP and HT, the studies were small (between 23 and 86 patients) with, as a consequence, a low number of outcomes. The percentage of HTs between studies showed a large variation (12–56%, depending on further selection), while percentages in daily practice are typically at the lower end of this range [3]. This might have caused an important selection bias, which makes the results less applicable for clinical use. Moreover, the duration of the CTP acquisition in most studies was relatively short (50–135s), which makes it questionable if they were truly measuring BBBP. Our study, with prospective inclusion of much larger number of patients suspected of acute ischemic stroke, uses a more robust model in combination with CTP acquisitions extended to 210 s, to assess BBBP. The number of HTs in our study is also much larger than in all other studies (57 vs. 3–27).

Most of the imaging variables used to predict HT relate to a large area of the brain. It is probably difficult to predict HT with those parameters as HT originates in a small area of the infarct, of which the location is difficult to determine in advance. The averaging with the normal values in the surrounding area could obscure higher values in this small area, whereas the local signal may be too weak to allow for visual detection. Measurement of BBBP remains complex due to the inherent problems with the low contrast to noise ratio in an ischemic area and movement artifacts on the extended CTP. The images may be difficult to interpret and the differentiation between focal abnormalities and imaging (noise) artifacts has been shown to be a challenge, relying on thresholds or comparison of brain areas or hemispheres. Prediction with BBBP could be improved by enhancing detector calibration to reduce the ring shaped scanner artifacts which are a cause of noise, and the use of more sophisticated iterative reconstruction techniques to reduce artifacts and increase the signal to noise ratio [24].

Strengths of this study are the prospective inclusion of a large population of suspected ischemic stroke patients analyzed with a BBBP method that proved to be more accurate than the commonly used linear Patlak method, and the combined use of clinical, NCCT, CTA, and CTP parameters.

This study also has limitations. First, the number of exclusions due to technical processing difficulties with an extended CTP was rather high (19%), but this could be reduced by techniques described above. As the percentage and types of HT are comparable in all DUST patients with follow-up imaging, it is unlikely that this has changed our results.

Second, the number of PH-2 type HT in our population was too small for sub-analysis. This is unfortunate, as PH-2 is a major determinant of poor outcome. However, smaller HTs have also been implicated in worse longer term clinical outcome [1, 2]. This means our results are not only directly transferable to the PH-2 population in particular, but nonetheless important for HT prediction in general.

Third, a small percentage of follow-up was performed with MRI instead of CT imaging. It is known that MRI is more sensitive in detecting smaller HT [34]. In contrast, the percentage of smaller HT (HI-1 and HI-2) in our population was not higher in patients with MRI follow-up compared to patients with CT follow-up, which makes bias due to a difference in modalities unlikely.

Conclusion

BBBP measurements, estimated by means of nonlinear regression, are related to the occurrence of HT in acute ischemic stroke, but do not improve prediction of HT with age and admission NIHSS. The technique of BBBP measurements requires further improvement before it can be a useful addition to decision making in patients considered for IV-rtPA treatment.

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Disclosures Statement

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