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Multi-center prediction of hemorrhagic transformation in acute ischemic stroke using permeability imaging features

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ABSTRACT

Permeability images derived from magnetic resonance (MR) perfusion images are sensitive to blood–brain barrier derangement of the brain tissue and have been shown to correlate with subsequent development of hemorrhagic transformation (HT) in acute ischemic stroke. This paper presents a multi-center retrospective study that evaluates the predictive power in terms of HT of six permeability MRI measures including contrast slope (CS), final contrast (FC), maximum peak bolus concentration (MPB), peak bolus area (PB), relative recirculation (rR), and percentage recovery (%R). Dynamic T2*-weighted perfusion MR images were collected from 263 acute ischemic stroke patients from four medical centers. An essential aspect of this study is to exploit a classifier-based framework to automatically identify predictive patterns in the overall intensity distribution of the permeability maps. The model is based on normalized intensity histograms that are used as input features to the predictive model. Linear and nonlinear predictive models are evaluated using a cross-validation to measure generalization power on new patients and a comparative analysis is provided for the different types of parameters. Results demonstrate that perfusion imaging in acute ischemic stroke can predict HT with an average accuracy of more than 85% using a predictive model based on a nonlinear regression model. Results also indicate that the permeability feature based on the percentage of recovery performs significantly better than the other features. This novel model may be used to refine treatment decisions in acute stroke.

1. Introduction

At present, acute ischemic stroke is treated with mechanical clot-retrieval devices and/or pharmaceutical recanalization therapies with the ultimate goal of restoring blood perfusion in the affected area and saving the endangered tissue. While a successful recanalization of the vessel improves the chances of recovery, critical complications such as intracerebral hemorrhage may result. A general guideline to reduce those risks is to limit the administration of thrombolytic therapy with recombinant tissue plasminogen activator (tPA) to patients admitted within 4.5 h of symptoms onset. This restrictive time-window aims primarily at reducing the risk of hemorrhagic transformation (HT) due to disruption of the blood–brain barrier (BBB) which is known to increase over time. HT, and intracranial hemorrhage in general, causes blood to accumulate within the brain, and may lead to devastating consequences as they may trigger potentially deadly increase of intracranial pressure (ICP).

This study focuses on the automatic prediction of HT in acute ischemic stroke from MRI images acquired at day 0. The administration of tPA constitutes a major cause of HT as it has been reported [1] that there is a 5.9% risk of HT associated with patients treated with tPA compared to 1.1% for controls. But the relationship is complex, other factors also come into play; previous studies [2] have identified clinical variables that may be linked to HT after tPA treatment. In addition, imaging studies based on multi-modal MRI are also promising as they provide unique insights regarding tissue status and potential risks for HT. For example, it has been shown that the volume of diffusion and perfusion abnormality is linked to an increased risk of HT after recanalization therapy [3–5]. Other

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imaging studies have found a variety of features correlated with an increased risk of HT, such as: low mean apparent diffusion coefficient (ADC) [3], reduced cerebral blood volume (CBV) or flow (CBF) [6,7], leukoaraiosis [8], prior microbleeds [9], early parenchymal enhancement [5], large vessel circle of Willis occlusion [10], poor collateral vessels on CT angiography [11], and early colony-stimulating factor hyperintensity [12].

It has been suggested [13] that HT may result from reperfusion into a large volume of ischemic tissue. It is possible to identify certain BBB permeability derangements in patients with acute ischemic stroke using dedicated MRI acquisitions. More recently, however, specific permeability parameters [14] derived from perfusion-weighted images (PWI) were computed before treatment and were shown to identify patients at risk for HT. The identification of BBB compromise relies on the fact that, during a PWI scan, the intensity of T2* signal decreases with bolus passage through the cerebrovasculature followed by a return to baseline intensity. In some areas, signal intensity may demonstrate a later decline at the terminal phase of scan acquisition; a synonym of continued increase in the concentration of the contrast agent. Late signal intensity changes at the terminal phase of scan acquisition may indicate accumulation of contrast within a region, rather than the expected return to baseline signal intensity after contrast clearance. Such an accumulation may be produced by slow leakage of contrast. In patients with BBB compromise, the contrast agent will leak out of the vasculature into surrounding tissue, which will result in persisting or even falling T2* intensity. In recent years, several permeability imaging features [15–19,14] extracted from T2* PWI images and reflecting this phenomenon have been introduced and have been shown to provide distinctive markers to identify patients with an increased risk of HT.

This study relies on these findings and evaluates six previously introduced T2* permeability imaging features (relative recirculation (rR), percentage recovery (%R), post-bolus area (PB), mean post-bolus intensity (MPB), contrast slope (CS), final contrast (FC)) on a large set of 263 patients treated for acute ischemic stroke in four different ischemic centers. To the best of our knowledge, this is the first multicenter study that evaluates the significance of these six permeability maps in predicting HT. It uses a large set of patients to more precisely assess the possibility of predicting HT from onset PWI images. A key technical contribution of the proposed statistical framework is to train classifier-based predictive model that uses histogram-based descriptor to summarize the distribution of the parameter intensity across the two hemispheres. The interventional decision-making process may benefit from a predictive model of HT by supplementing standard diffusion and perfusion MRI imaging parameters with predicted maps of HT based on permeability imaging.

2. Methods

2.1. Patients and MRI data acquisition

The multi-center collaborative imaging study presented in this paper was conducted on 277 patients admitted to an intensive care unit (ICU) for acute ischemic stroke. The four following centers were involved in the study: Stroke Diagnostics and Therapeutics, NIH, Bethesda, MD (95 patients); University of Calgary Medicine, Calgary, AB, Canada (79 patients); University of California Los Angeles (UCLA) Stroke Center, Los Angeles, CA (78 patients); Institute of Neurosciences and Psychology, University of Glasgow, Glasgow, United Kingdom (25 patients). The use of this data was approved by the local Institutional Review Board (IRB).

Inclusion criteria for this retrospective study were: (1) diagnosis of acute ischemic stroke, (2) PWI of the brain performed at day 0, (3) HT assessed 24 h after intervention. A stroke neurologist (D.S.L.) from UCLA retrospectively examined gradient-recalled echo (GRE) (and any other images available) for signs of HT. The expert was blinded to PWI permeability images and asked to subdivide HT into 4 types according to previously described definitions [20]: HI1, HI2 (Petechiae within the infarcted area), PH1 or PH2 (parenchymal hematoma with extensive hemorrhage). Among the 277 patients considered, 14 were discarded due to either short scan acquisition times, artifact due to patient movement, or failed image processing. The demographics of the 263 selected patients who satisfied the above-mentioned criteria are summarized in Table 1. They had a mean age of 69±15 years, 153 were women, and baseline median NIHSS was 10 (range, 0–40). All patients underwent MRI before possible recanalization therapy. T2*-MRI sequences were acquired as part of routine imaging evaluation at a median of 214 min from symptom onset. Treatments included IV tPA alone (129), endovascular recanalization alone (55), and both in 27 cases. Overall, HT on gradient-echo (GRE) images at 24 h was observed in 84 (31.9%), including 34 HI1, 30 HI2, 9 PH1 and 11 PH2.

Because of the multicentric origin of the data, image acquisition parameters vary across subjects. The MRI protocol (at 1.5 or 3 T) included T2* perfusion-weighted imaging (PWI) sequences at onset. PWI was performed with a timed contrast bolus passage technique (0.1 mg/kg contrast administered into an antecubital vein with a power injector at a rate of 5 cm^3/s). The PWI parameters were as follows (median, minimum, maximum): repetition time, 2000 ms (from 1400 to 4000 ms); TE, 45 ms (from 21.6 to 65 ms); slice thickness, 5 mm (from 4 to 7 mm); no gap; matrix size, 128 × 96 to 256 × 256; and field of view, 240 mm. Post-intervention gradient-recalled echo (GRE) was acquired with repetition time, 800 ms; TE, 15 ms. The analysis was confined to cases with sufficient scan acquisition times (>60 s) to permit BBB leakage to be discerned from analysis of late transit phases of gadolinium passage associated with contrast bolus.

2.2. Permeability Features From Perfusion MRI (PWI)

PWI source images are processed retrospectively to extract specific permeability imaging features used as surrogate for risks of HT using previously introduced image processing algorithms [19,14]. A total of six *T2**-based permeability feature maps are extracted from the contrast concentration-versus-time curve using the Stroke Cerebral Analysis (SCAN) software developed in our imaging laboratory. The features included in this study were selected because they demonstrated significant correlation with development of HT in previous works; they are relative recirculation (rR), percentage recovery (%R), post-bolus area (PB), mean post-bolus intensity (MPB), terminal slope of concentration curve (CS), final contrast (FC).

Features are estimated for each voxel of the brain volume using the concentration–time curve ΔR^{2*} [21] (an illustrative example from simulated data is shown in Fig. 1) derived from the measured image intensity I,

$$\Delta R^{2*}(t) = -\ \mathrm{TE}^{-1} ln\left(\frac{I(t)}{I(0)}\right) \quad (1)$$

Table 1
Demographic information from 263 patients with Acute Ischemic Stroke.

Patient Demographics	
Characteristic	Value
Gender	110 men, 153 women
Age	69 ± 15
NIHSS	10 (0–40)
Imaging time	258 min (33–1620 min)
Treatment	IV tPA (129), endovascular recanalization (55), both (27)
Number of HT	84 (31.9%)
Type of HT	HI1 (34), HI2 (30), PH1 (9), and PH2 (11)