Apoplipoprotein E Genotype Is Associated With CT Angiography Spot Sign in Lobar Intracerebral Hemorrhage

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Background and Purpose—The CT angiography (CTA) spot sign predicts hematoma expansion and poor outcome in patients with primary intracerebral hemorrhage (ICH). The biological underpinnings of the spot sign remain poorly understood; it may be that the underlying vasculopathy influences its presence. Therefore, we conducted a study to identify genetic predictors of the spot sign.

Methods—In an ongoing prospective cohort study, we analyzed 371 patients with CTA and genetic data available. CTAs were reviewed for the spot sign by 2 experienced readers, blinded to clinical data, according to validated criteria. Analyses were stratified by ICH location.

Results—In multivariate analysis, patients on warfarin were more likely to have a spot sign regardless of ICH location (OR, 3.85; 95% CI, 1.33–11.13 in deep ICH and OR, 2.86; 95% CI, 1.33–6.13 in lobar ICH). Apolipoprotein E ε2, but not ε4, was associated with the presence of a spot sign in lobar ICH (OR, 2.09; 95% CI, 1.05–4.19). There was no effect for ε2 or ε4 in deep ICH.

Conclusions—Patients with ICH on warfarin are more likely to present with a spot sign regardless of ICH location. Among patients with lobar ICH, those who possess the apolipoprotein E ε2 allele are more likely to have a spot sign. Given the established relationship between apolipoprotein E ε2 and vasculopathic changes in cerebral amyloid angiopathy, our findings suggest that both hemostatic factors and vessel pathology influence spot sign presence. (Stroke. 2012;43:00-00.)

Key Words: APOE ■ CTA spot sign ■ genetics ■ hematoma expansion ■ intracerebral hemorrhage

Spontaneous intracerebral hemorrhage (ICH) accounts for 15% of all strokes and has a 30-day mortality rate of approximately 40%.1,2 The most potent determinant of poor outcome is baseline hematoma volume.3 Importantly, expansion of the initial hematoma occurs in 25% of hospitalized patients with ICH and forms another strong predictor of poor outcome.4,5 The attenuation of hematoma expansion gives clinical care providers an opportunity to decrease final ICH volume and is therefore a common target in ongoing clinical trials.6,7

The extravasation of contrast into the hematoma after CT angiography (CTA), termed the “spot sign,” is frequently seen in patients with ICH and is an independent predictor of both hematoma expansion8–10 and poor outcome.11–13 The biological underpinnings of the CTA spot sign remain poorly understood, and there are no established risk factors for its presence besides early presentation.10,13,14

A multicenter genetic association study led by the International Stroke Genetics Consortium showed that apolipoprotein E (APOE) ε2 and ε4 alleles increase risk of lobar intracerebral hemorrhage.15 In addition, the APOE ε2 allele has been associated with larger baseline ICH volumes,16 hematoma expansion,17 and poor outcome18 in lobar ICH. The role of the APOE alleles is probably related to their known effect in cerebral amyloid angiopathy (CAA),18 in which each allele is associated with characteristic pathologic changes. The ε2 allele is predominantly associated with vasculopathic changes ultimately leading to rupture of the diseased vessels, whereas ε4 increases the severity of amyloid deposition within the vessel wall.19,20

Given the unique role of APOE ε2 in lobar ICH, we hypothesized that the ε2 allele would also be associated with the presence of the CTA spot sign. To answer this question, we conducted a single-center prospective cohort study of patients with acute ICH.

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Methods

Study Design
This study is a retrospective analysis of prospectively collected data from an ongoing cohort study at Massachusetts General Hospital, Boston, MA. All parts of the study were approved by the Institutional Review Board of Massachusetts General Hospital and informed consent was obtained from all participants or their families/surrogates.

Study Subjects
Consecutive patients with acute primary ICH who presented between December 2000 and January 2011 to Massachusetts General Hospital and who met inclusion criteria were approached for enrollment in an ongoing genetic ICH study. The inclusion criteria for this analysis were defined as: (1) diagnosis of nontraumatic ICH on CT; (2) availability of a baseline CTA; (3) self-reported European or European–American ancestry; and (4) APOE genotype data available. For a subgroup analysis, patients with an available follow-up CT scan within 48 hours of the baseline CT were included. Exclusion criteria were defined as: presence of a vascular malformation, aneurysmal subarachnoid hemorrhage, hemorrhagic transformation of acute infarction, traumatic ICH, brain neoplasm, or any other suspected cause of secondary ICH. Patients with ICH of the brainstem or primary intraventricular hemorrhage were also excluded from the current analysis. (Figure)

Clinical Data
Collected data included age, sex, and medical history including diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation, hyperlipidemia, ischemic stroke, and previous ICH. Medications included the use of warfarin, antiplatelet therapy, and statins. All data points were collected through interviews with the patient or their families/surrogates. Hospital charts were reviewed for Glasgow Coma Scale, time to initial imaging, and interscan time for patients with a follow-up CT available.

CT Analysis
ICH location was assigned by trained study staff based on the baseline CT. Deep ICH was defined as ICH exclusively involving thalamus or basal ganglia, whereas ICH originating at the cortical-subcortical junction was considered lobar ICH. For this analysis, hemorrhages involving both territories were labeled as mixed ICH.

The initial and follow-up volumes of both ICH and intraventricular hemorrhage were measured using Alice (PAREXEL International Corporation) and Analyze 9.0 (Mayo Clinic, Rochester, MN) software following previously described methods. Significant hematoma expansion was defined as an absolute increase in ICH volume >6 mL or an increase of >33% from baseline ICH volume. CTAs were reviewed by 2 experienced readers, blinded to clinical data, for the presence of spot signs according to previously published and validated criteria. CTA reading differences were adjudicated by consensus. All study staff interpreting neuroimaging were blinded to clinical, genetic, and outcome data.

Genotyping
DNA from whole blood samples was isolated, quantified, and normalized to a concentration of 10 ng/μL. Two single nucleotide polymorphisms of the APOE locus, rs7412 (APOE 158) and rs429358 (APOE 112), were independently genotyped using 2 separate assays. The allelic reads from each assay were translated to APOE genotypes (ε3ε3, ε3ε4, ε4ε4, ε3ε2, ε2ε2, and ε2ε4). All ICH cases were in Hardy-Weinberg equilibrium for APOE genotypes. Genotyping personnel were blinded to clinical and neuroimaging data.

CAA-Related ICH
Along with stratifying the analysis by ICH location, we separately analyzed patients meeting criteria for probable/definite CAA (according to the Boston criteria), because not all lobar hemorrhages are caused by CAA. Lobar ICH with confirmed CAA pathology or microbleeds restricted to the lobar brain region on MRI (on T2*, susceptibility, or gradient echo sequences) was defined as probable/definite CAA. In total, 140 of 196 (71%) patients with lobar ICH had MRI and/or pathology available. Of these patients, 69 (49%) met criteria for probable/definite CAA. Microbleed assessment was performed following previously validated methods.

Statistical Analysis
Discrete variables are presented as count and percentage (%) and continuous variables are shown as mean and SD or as median and interquartile range. We tested the potential role of the APOE ε2 and ε4 alleles as predictors of the CTA spot sign using univariate and multivariate logistic regression, stratified by ICH location (deep or lobar) and CAA-related ICH. This stratification was prespecified and used in previous studies. The CTA spot sign was analyzed as a dichotomized variable (present/absent). Multivariate models included age, sex, hypertension, use of warfarin, number of APOE ε2 alleles (0, 1, or 2), and number of ε4 alleles (0, 1, or 2). All analyses were repeated after adjustment for genetic population structure (principal components 1 and 2) based on genomewide data, which was available for a total of 268 patients. These subset analyses returned identical results (data not shown). In a subset of patients with an available follow-up CT within 48 hours, we tested for association of the APOE alleles with hematoma expansion.
expansion, including the same covariates in the multivariate analysis with the addition of the CTA spot sign. The threshold of significance was set to $P<0.05$. All statistical analyses were performed using Statistical Analysis Software Version 9.3 (SAS Institute Inc, Cary, NC).

Results

Study Population

After application of the previously described inclusion and exclusion criteria, 371 patients were available for analysis. Of these 371 patients, 151 had deep, 196 had lobar, and 24 had mixed ICH. The latter were excluded for the stratified analysis (Table 1).

CT Imaging

Radiographic characteristics are shown in Table 1 for the entire cohort and stratified by ICH location. Median baseline hematoma volumes were significantly different between deep and lobar ICH ($P<0.001$). At least 1 spot sign was present in 97 patients (26%), and there was no difference between deep and lobar ICH ($P>0.20$; Table 1).

Predictors of the CTA Spot Sign

All ICH

Univariate analysis was performed to assess association of the covariates with CTA spot sign presence in all patients with ICH. Both age ($P=0.033$) and warfarin use at the time of hospital presentation ($P<0.001$) showed an association with the spot sign (Table 2). In multivariate analysis, only warfarin use remained associated with spot sign presence ($P<0.001$) after adjusting for age, sex, hypertension, warfarin use, APOE ε2, APOE ε4, and genetic population structure (Table 3).

Deep ICH

In deep ICH only warfarin showed an association with spot sign presence ($P=0.007$) in univariate analysis (Table 2). In multivariate analysis, this association remained significant

Table 1. Cohort Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All, No. (%)</th>
<th>Deep ICH, No. (%)</th>
<th>Lobar ICH, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>371</td>
<td>151</td>
<td>196</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>72.6 (12.8)</td>
<td>68.6 (14.3)</td>
<td>75.9 (10.7)</td>
</tr>
<tr>
<td>Female sex</td>
<td>180 (48.5)</td>
<td>65 (43.0)</td>
<td>102 (52.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>77 (20.8)</td>
<td>40 (26.5)</td>
<td>29 (14.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>289 (77.9)</td>
<td>132 (87.4)</td>
<td>133 (67.9)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>69 (18.6)</td>
<td>31 (20.5)</td>
<td>33 (16.8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>78 (21.0)</td>
<td>23 (15.2)</td>
<td>50 (25.5)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>150 (40.4)</td>
<td>59 (39.1)</td>
<td>85 (43.4)</td>
</tr>
<tr>
<td>Pre-ICH ischemic stroke</td>
<td>41 (11.1)</td>
<td>14 (9.3)</td>
<td>21 (10.7)</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>69 (18.6)</td>
<td>21 (13.9)</td>
<td>43 (21.9)</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>22 (5.9)</td>
<td>11 (7.3)</td>
<td>11 (5.6)</td>
</tr>
<tr>
<td>Statin use</td>
<td>120 (32.3)</td>
<td>46 (30.5)</td>
<td>69 (35.2)</td>
</tr>
<tr>
<td>Probable/definite CAA</td>
<td>70 (18.9)</td>
<td>0 (0.0)</td>
<td>69 (35.2)</td>
</tr>
<tr>
<td>GCS, median (IQR)</td>
<td>14 (7–15)</td>
<td>12 (6–15)</td>
<td>14 (7–15)</td>
</tr>
<tr>
<td>Time to baseline imaging, h, median (IQR)</td>
<td>6.0 (3.0–13.0)</td>
<td>5.0 (3.0–9.0)</td>
<td>6.0 (4.0–17.0)</td>
</tr>
<tr>
<td>Baseline ICH volume, median (IQR)</td>
<td>24.4 (8.0–59.0)</td>
<td>17.9 (5.4–44.6)</td>
<td>36.0 (16.3–71.6)</td>
</tr>
<tr>
<td>Follow-up ICH volume, median (IQR)*</td>
<td>19.0 (6.2–42.8)</td>
<td>12.8 (4.1–35.3)</td>
<td>27.1 (11.5–52.0)</td>
</tr>
<tr>
<td>Intraventricular extension</td>
<td>182 (49.1)</td>
<td>89 (58.9)</td>
<td>80 (40.0)</td>
</tr>
<tr>
<td>Baseline IVH volume, median (IQR)†</td>
<td>7.7 (2.2–24.0)</td>
<td>15.0 (3.2–35.0)</td>
<td>6.5 (2.3–17.8)</td>
</tr>
<tr>
<td>Follow-up IVH volume, median (IQR)*</td>
<td>6.5 (2.0–21.3)</td>
<td>11.0 (3.4–24.5)</td>
<td>4.0 (2.0–13.0)</td>
</tr>
<tr>
<td>Interscan time, h, median (IQR)*</td>
<td>10.0 (6.0–17.0)</td>
<td>9.0 (6.0–14.5)</td>
<td>12.0 (6.3–18.0)</td>
</tr>
<tr>
<td>Spot sign presence</td>
<td>97 (26.1)</td>
<td>41 (27.2)</td>
<td>52 (26.5)</td>
</tr>
<tr>
<td>Hematoma expansion, (&gt;6 mL or &gt;33%)*</td>
<td>42 (18.4)</td>
<td>19 (20.2)</td>
<td>23 (16.7)</td>
</tr>
<tr>
<td>Death at 90 d</td>
<td>156 (42.0)</td>
<td>63 (41.7)</td>
<td>93 (47.4)</td>
</tr>
<tr>
<td>mRS at 90 d (0–2)‡</td>
<td>106 (31.0)</td>
<td>37 (26.4)</td>
<td>60 (32.3)</td>
</tr>
<tr>
<td>APOE ε2 (minor allele frequency)</td>
<td>0.09</td>
<td>0.08</td>
<td>0.11</td>
</tr>
<tr>
<td>APOE ε4 (minor allele frequency)</td>
<td>0.19</td>
<td>0.17</td>
<td>0.22</td>
</tr>
</tbody>
</table>

ICH indicates intracerebral hemorrhage; CAA, cerebral amyloid angiopathy; GCS, Glasgow Coma Scale; IQR, interquartile range; IVH, intraventricular hemorrhage; mRS, modified Rankin Scale; APOE, apolipoprotein E.

*Among patients who had a follow-up CT within 48 hours (61%).
†Data refers only to ICH cases with intraventricular extension.
‡Among patients with available 3-mo follow-up (92%).
(P=0.013). There was no association between either APOE e2 or e4 and spot sign presence (both P>0.20; Table 3).

**Lobar ICH**

In lobar ICH, the univariate analysis showed warfarin use (P=0.001) and APOE e2 (P=0.025) to be associated with spot sign presence (Table 2). After adjusting for potential confounders, the effect for the use of warfarin (P=0.007) and APOE e2 (P=0.036) remained significant. We found again no association between APOE e4 and the CTA spot sign (P>0.20; Table 3).

**CAA-Related ICH**

In the subset of patients with lobar ICH meeting criteria for CAA-related ICH, warfarin use (P=0.011) and APOE e2 (P=0.024) were associated with spot sign presence in the univariate analysis (Table 2). In multivariate analysis, the effect for APOE e2 remained significant after adjusting for potential confounders (P=0.005). The effect for warfarin use in lobar ICH (OR, 2.86; 95% CI, 1.33–6.13) appeared heightened in patients meeting criteria for CAA-related ICH (OR, 6.65; 95% CI, 1.34–32.99).

**Predictors of Hematoma Expansion**

A follow-up CT within 48 hours was available in a subset of 228 patients (61%). Patients without follow-up imaging had lower Glasgow Coma Scale scores upon presentation, greater hematoma volumes, and higher mortality rates at discharge (all P<0.05).

Hematoma expansion was present in 42 of 228 patients (18%). In multivariate analysis, the spot sign was a strong independent predictor of hematoma expansion regardless of ICH location. Notably, warfarin use was no longer associated with hematoma expansion after introducing the CTA spot sign into the multivariate logistic regression model (all P>0.20). In lobar ICH, there was a trend toward significance for the association of APOE e2 and hematoma expansion (OR, 2.48; 95% CI, 0.99–6.27; P=0.054; Table 4).

**Discussion**

Our findings demonstrate that patients with lobar ICH who posses the APOE e2 allele are more likely to have a spot sign detected on CTA. APOE e2 did not show an effect in deep ICH and the APOE e4 allele was not associated with spot sign presence in either deep or lobar ICH. In addition, we show that patients on warfarin at the time of their presentation to the hospital are more likely to have a spot sign regardless of ICH location.

The isolated effect of APOE e2 on presence of the CTA spot sign is consistent with the accumulating evidence of the unique effects of the APOE alleles in CAA and ICH. In CAA, the 2 APOE Variants appear to act through different histopathologic mechanisms. At autopsy or biopsy, the cerebral vessels of individuals with APOE e2 demonstrate marked vasculopathic changes and vessel rupture, whereas possession of the e4 allele increases the severity of amyloid deposition within the vessel wall with limited vasculopathic changes. In addition to these histopathologic findings in CAA, there is growing evidence on the isolated APOE e2 effect in lobar ICH from prospective cohort studies. In these studies, APOE

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**Table 2. Univariate Analysis of CTA Spot Sign**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=371) OR (95% CI) P Value</th>
<th>Deep ICH (n=151) OR (95% CI) P Value</th>
<th>Lobar ICH (n=196) OR (95% CI) P Value</th>
<th>Probable/Definite CAA (n=69) OR (95% CI) P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02 (1.00–1.04) 0.05</td>
<td>1.02 (0.99–1.06) 0.14</td>
<td>1.02 (0.99–1.06) 0.17</td>
<td>1.08 (0.95–1.23) 0.20</td>
</tr>
<tr>
<td>Sex (male versus female)</td>
<td>1.34 (0.70–2.58) &gt;0.20</td>
<td>1.83 (0.81–4.16) 0.15</td>
<td>1.91 (0.90–3.95) &gt;0.20</td>
<td>1.46 (0.37–5.77) &gt;0.20</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.28 (0.65–2.56) &gt;0.20</td>
<td>0.81 (0.26–2.53) &gt;0.20</td>
<td>0.53 (0.19–1.53) &gt;0.20</td>
<td>1.64 (0.37–7.51) &gt;0.20</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>3.46 (1.92–6.21) &lt;0.001</td>
<td>3.85 (1.33–11.13) 0.013</td>
<td>2.86 (1.33–6.13) 0.007</td>
<td>6.65 (1.34–32.99) 0.020</td>
</tr>
<tr>
<td>APOE e2</td>
<td>1.55 (0.81–2.96) 0.19</td>
<td>0.53 (0.16–1.70) &gt;0.20</td>
<td>2.09 (1.05–4.19) 0.036</td>
<td>2.07 (1.24–3.46) 0.005</td>
</tr>
<tr>
<td>APOE e4</td>
<td>0.64 (0.33–1.25) &gt;0.20</td>
<td>0.70 (0.32–1.55) &gt;0.20</td>
<td>0.60 (0.26–1.36) &gt;0.20</td>
<td>0.77 (0.27–2.18) &gt;0.20</td>
</tr>
</tbody>
</table>

CTA indicates CT angiography; ICH, intracerebral hemorrhage; CAA, cerebral amyloid angiopathy; APOE, apolipoprotein E.

**Table 3. Multivariate Analysis of CTA Spot Sign**

<table>
<thead>
<tr>
<th>Variable*</th>
<th>All (n=371) OR (95% CI) P Value</th>
<th>Deep ICH (n=151) OR (95% CI) P Value</th>
<th>Lobar ICH (n=196) OR (95% CI) P Value</th>
<th>Probable/Definite CAA (n=69) OR (95% CI) P Value</th>
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<td>Sex (male versus female)</td>
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</tr>
<tr>
<td>APOE e2</td>
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<td>0.53 (0.16–1.70) &gt;0.20</td>
<td>2.09 (1.05–4.19) 0.036</td>
<td>2.07 (1.24–3.46) 0.005</td>
</tr>
<tr>
<td>APOE e4</td>
<td>0.64 (0.33–1.25) &gt;0.20</td>
<td>0.70 (0.32–1.55) &gt;0.20</td>
<td>0.60 (0.26–1.36) &gt;0.20</td>
<td>0.77 (0.27–2.18) &gt;0.20</td>
</tr>
</tbody>
</table>

*Analysis is also adjusted for principal components 1 and 2.
ε2 was associated with larger initial ICH volumes, hematoma expansion, and poor clinical outcome.16,17

The association between APOE ε2 and presence of the spot sign raises important hypotheses regarding the pathophysiology of this radiographic finding. If the spot sign reflects active extravasation of contrast into the hematoma, our findings fit within the proposed model of cascading small vessel injury after ICH.24 In this model, hematoma expansion occurs due to the additional rupture of small vessels adjacent to the initial hematoma. If this hypothesis holds true, the spot sign may be the visual representation of active hematoma expansion caused by the rupture of (diseased) vessels surrounding the initial hematoma. This aligns with the isolated effect of APOE ε2 on lobar rather than deep ICH; given its unique role in CAA, it would predispose to additional vessel rupture and therefore hematoma expansion and spot sign presence. The previously published association between APOE ε2 and lobar hematoma expansion also fits within this model.17

Thus far, therapies aimed at arresting hematoma expansion have not improved clinical outcome in clinical trials, likely due to difficulty selecting the right patients for inclusion. The development of biomarkers for hematoma expansion will improve our ability to guide the most aggressive treatments to those with the greatest opportunity to benefit. APOE genotyping may well be such a biomarker, because it is consistently associated with important measures in acute ICH including baseline hematoma volume, hematoma expansion, CTA spot sign, and clinical outcome.16,17 Bedside genotyping is on the verge of widespread availability, and potential uses may include risk stratification for hemostatic therapies and long-term anticoagulation use in those with ICH. Besides its potential role as a biomarker in acute ICH, at this point our findings on the APOE ε2 allele provide insight into the biological underpinnings of hematoma expansion and the epiphenomenon of the CTA spot sign.

Our study is limited by its lack of replication and the biased availability of follow-up CTS for the subgroup analysis. The latter is a recurring phenomenon, in which follow-up imaging is disproportionately not obtainable due to early death or care limitations in patients with the lowest Glasgow Coma Scale scores and largest hematomas. However, the baseline characteristics of patients with and without available CTA were not different in our study. Although our findings have not been replicated, the presented findings are in line with previous studies and generate interesting hypotheses regarding the pathophysiology of hematoma expansion. Further research on the role of APOE in ICH and replication of our results is necessary.

In conclusion, we show that the APOE ε2 allele is associated with the presence of the CTA spot sign in patients with lobar ICH. Patients on warfarin are also more likely to have a spot sign upon presentation regardless of ICH location. Given the established relationship between APOE ε2 and vasculopathic changes in CAA, our findings suggest that both hemostatic factors and vessel pathology influence the development of the spot sign and risk of prolonged bleeding in ICH.

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**Disclosures**

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References
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Abstract

Apolipoprotein E Genotype Is Associated With CT Angiography Spot Sign in Lobar Intracerebral Hemorrhage

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Apolipoprotein E (ApoE) genotype is associated with CT angiography spot sign in lobar intracerebral hemorrhage (ICH). ApoE ε2 and ε4 genotypes were significantly associated with an increased risk of CT angiography spot sign when compared to ApoE ε3 genotypes. These findings may have implications for the early identification of patients at risk for delayed hemorrhagic transformation.