

# Blend Sign on Computed Tomography Novel and Reliable Predictor for Early Hematoma Growth in Patients With Intracerebral Hemorrhage

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**Background and Purpose**—Early hematoma growth is not uncommon in patients with intracerebral hemorrhage and is an independent predictor of poor functional outcome. The purpose of our study was to report and validate the use of our newly identified computed tomographic (CT) blend sign in predicting early hematoma growth.

**Methods**—Patients with intracerebral hemorrhage who underwent baseline CT scan within 6 hours after onset of symptoms were included. The follow-up CT scan was performed within 24 hours after the baseline CT scan. Significant hematoma growth was defined as an increase in hematoma volume of >33% or an absolute increase of hematoma volume of >12.5 mL. The blend sign on admission nonenhanced CT was defined as blending of hypoattenuating area and hyperattenuating region with a well-defined margin. Univariate and multivariable logistic regression analyses were performed to assess the relationship between the presence of the blend sign on nonenhanced admission CT and early hematoma growth.

**Results**—A total of 172 patients were included in our study. Blend sign was observed in 29 of 172 (16.9%) patients with intracerebral hemorrhage on baseline nonenhanced CT scan. Of the 61 patients with hematoma growth, 24 (39.3%) had blend sign on admission CT scan. Interobserver agreement for identifying blend sign was excellent between the 2 readers ( $\kappa=0.957$ ). The multivariate logistic regression analysis demonstrated that the time to baseline CT scan, initial hematoma volume, and presence of blend sign on baseline CT scan to be independent predictors of early hematoma growth. The sensitivity, specificity, positive and negative predictive values of blend sign for predicting hematoma growth were 39.3%, 95.5%, 82.7%, and 74.1%, respectively.

**Conclusions**—The CT blend sign could be easily identified on regular nonenhanced CT and is highly specific for predicting hematoma growth. (*Stroke*. 2015;46:2119-2123. DOI: 10.1161/STROKEAHA.115.009185.)

**Key Words:** cerebral hemorrhage ■ computed tomography ■ diagnostic imaging ■ hematoma ■ stroke

Intracerebral hemorrhage (ICH) is a devastating neurological disorder that accounts for  $\approx 10\%$  to  $30\%$  of all strokes.<sup>1</sup> It is the least treatable form of stroke and is associated with high morbidity and mortality. Initial ICH volume and hematoma location are strong predictors of 30-day mortality and functional outcome.<sup>2,3</sup> However, the volume and location of the hematoma is unmodifiable predictors on presentation. Early hematoma growth is a modifiable factor that is highly predictive of neurological deterioration in patients with ICH.

Hematoma growth, which is defined as hematoma growth >33% or 12.5 mL on follow computed tomographic (CT) scan, is frequently observed in patients with spontaneous ICH.<sup>4</sup> Hematoma growth has been reported in  $\approx 30\%$  of patients presenting within 6 hours of symptom onset and is an independent predictor of poor functional outcome.<sup>5-7</sup>

Recently, imaging marker for hematoma growth has been identified on computed tomographic angiography (CTA). It is

well documented that the presence of enhancing foci of contrast extravasation or the CTA spot sign may predict hematoma growth and is associated with poor functional outcome.<sup>8,9</sup> Although the CTA spot sign is a promising imaging predictor of hematoma growth, the recognition of the spot sign requires early CTA examination, which is relatively expensive and not readily available in all clinical settings. Identification of novel imaging predictors of hematoma growth is crucial for early therapeutic intervention.

The noncontrast CT scan is the standard first line imaging method of choice for patients with ICH. It is fast, affordable, and widely available. In our study, we have identified a novel blend sign on admission nonenhanced CT that could be used to predict early hematoma growth in patients with ICH. The aim of our study was to investigate the clinical use of our newly identified CT blend sign in predicting early hematoma growth in patients with ICH.

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## Materials and Methods

### Patients

Institutional Review Board approval was obtained. Patients aged >18 years with spontaneous ICH who underwent baseline and follow-up CT scan in our institution between May 2011 and January 2015 were retrospectively included into our study. ICH was confirmed on nonenhanced CT scan showing parenchymal bleeding. Patients were excluded from our study if surgery was performed before the follow-up CT scan. Patients were also excluded from the study if they had head trauma, brain tumor, or secondary ICH from hemorrhagic transformation of brain infarction. Patients were excluded from the study if they have undergone surgical evacuation of hematoma before the follow-up CT scan. We have excluded patients receiving anticoagulants therapy before onset of ICH. The patients were diagnosed by baseline CT within 6 hours after onset of symptoms and follow-up CT scans were performed at 24 hours after the initial CT scan. The demographic information and the time to baseline and follow-up CT scans were recorded for each participant.

### Imaging Analysis

The admission and follow-up CT scans were performed using standard clinical parameters with axial 5-mm section thickness. The images were obtained and stored for further evaluation. The location of the hematoma was assessed and documented. The hemorrhage locations were classified as basal ganglia, thalamus, lobe, brain stem, and cerebellum. On the basis of the criteria used in several large clinical studies of ICH, we have defined hematoma growth as an increase in hematoma volume of >33% or >12.5 mL at follow-up CT scan. Two experienced reviewers, who were blinded to the clinical information of the patients, independently evaluated the presence of the blend sign. Discrepancies about the occurrence of blend sign were settled by joint discussion of the 2 readers. The hematoma blend sign was defined as (1) blending of relatively hypoattenuating area with adjacent hyperattenuating region within a hematoma; (2) there is a well-defined margin between the hypoattenuating area and adjacent hyperattenuating region that is easily recognized by the naked eye; (3) the hematoma should have at least a 18 Hounsfield unit difference between the 2 density regions; (4) the relatively hypoattenuating area was not encapsulated by the hyperattenuating region. The hematoma has to meet the 4 criteria mentioned above to be defined as blend sign. The hypoattenuating area may vary in shape and size, but it should have a clearly defined border and is easily recognized by the naked eye. The imaging features of typical blend sign and blend sign mimics are illustrated in Figure 1.

### Statistical Analysis

All statistical analyses were performed by using a commercially available software package (SPSS, Version 19.0.). Categorical data are presented as proportions and continuous variables were presented as mean±SDs. The demographic, clinical, and radiological characteristics were compared between patients with hematoma growth and those without expansion by using Fisher exact test, and student *t* test as appropriate. A *P*<0.05 was considered statistically significant. Independent association of the CT blend sign and significant hematoma growth was evaluated by using multivariable logistic regression. The receiver–operator analysis was performed to assess the value of blend sign in predicting hematoma growth. The interobserver reliability of the blend sign was assessed by calculation of  $\kappa$  values. The  $\kappa$  values were categorized as follows:  $\kappa$ =0.21 to 0.4, 0.41 to 0.6, 0.61 to 0.8, and 0.81 to 1 indicate low, moderate, substantial, and excellent agreement between observers. A  $\kappa$ =1 indicates total agreement between observers.

## Results

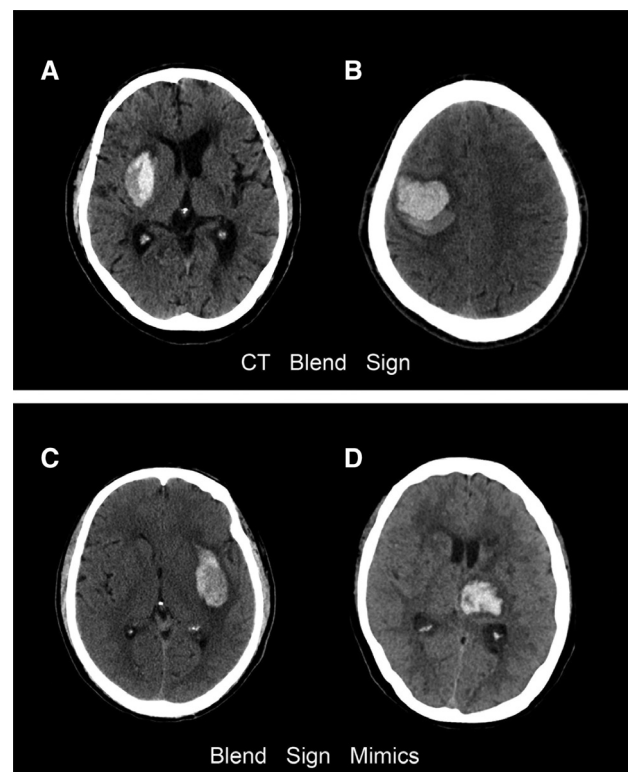
### Baseline Characteristics

A total of 172 patients were included in our study. There were 117 men and 55 women. The mean age of the patients was 61±12 years (age range, 31–87 years). Significant hematoma

growth was observed in 61 patients (35%) with ICH. The average baseline hematoma volume was 17.1 mL. The average time to baseline CT scan was 2.3 hours from the onset of symptoms. The baseline hematoma was located in basal ganglia (59.3%), thalamus (25%), cerebral lobes (10.5%), brain stem (2.9%), and cerebellum (2.3%). The baseline clinical characteristics of patients with and without significant hematoma growth were listed in Table 1. There were no statistically significant differences in age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, and alcohol drinking.

### Prevalence and Interobserver Agreement of Blend Sign

Blend sign was observed in 29 of 172 (16.9%) patients with ICH on baseline nonenhanced CT scan. Of the 61 patients with hematoma growth, 24 (39.3%) had blend sign on admission CT scan. Interobserver agreement for identifying blend sign was excellent between the 2 readers ( $\kappa$ =0.957). Discrepancies were observed in 2 patients between the 2 readers. The sensitivity, specificity, positive and negative predictive values of blend sign for predicting hematoma growth were 39.3%, 95.5%, 82.7%, and 74.1%, respectively. The receiver–operator analysis was performed and confirmed the value of blend sign



**Figure 1.** Illustration of computed tomographic (CT) blend sign and blend sign mimics. Axial nonenhanced CT images of 4 patients with CT blend sign and blend sign mimics. **A** and **B**, Different forms of CT blend sign in patients with putaminal and lobar hemorrhages. Note that the blend sign is composed of 2 parts with apparently different CT attenuation. There is a well-defined margin between the 2 regions. **C**, Heterogeneous looking putaminal hematoma without a well-defined margin between the hyperattenuated and relatively hypoattenuated regions. **D**, Hypointense region within a hyperattenuating hematoma which is consistent with a CT swirl sign.

**Table 1. Comparison of Baseline Demographic, Clinical, and Radiological Characteristics Between Patients With and Without Hematoma Growth**

Characteristics	Expander (n=61)	Nonexpander (n=111)	P Value
Mean age, yr (SD)	62.1 (11.6)	59.5 (12.2)	0.164
Sex, male (%)	46 (75.4%)	71 (64%)	0.171
Alcohol consumption (%)	28 (45.9%)	51 (45.9%)	0.996
Smoking (%)	32 (52.5%)	46 (41.4%)	0.167
Hypertension (%)	43 (70.5%)	73 (65.8%)	0.527
Diabetes mellitus (%)	9 (14.8%)	14 (12.6%)	0.815
Time to baseline CT (SD)	1.67 (1.17)	2.76 (1.72)	<0.001
Baseline hematoma volume (SD)	24.31 (20.68)	13.12 (8.08)	<0.001
Blend sign on baseline CT (%)	24 (39.3%)	5 (4.5%)	<0.001

CT indicates computed tomography.

in predicting hematoma growth (area under the curve=0.674;  $P<0.001$ ; Figure 2).

The baseline clinical and radiological variables of patients with and without CT blend sign were compared and listed in Table 2. The age, sex, history of hypertension, diabetes mellitus, smoking history, and alcohol consumption were similar between patients with CT blend sign and those without the blend sign ( $P>0.05$ ). The baseline hematoma volume of patients with blend sign was significantly larger compared with those without the sign ( $P<0.01$ ).

Univariate logistic regression analysis was performed to assess the association between various clinical and radiological parameters and early hematoma growth. In the univariate logistic analysis, the time to baseline CT scan, initial hematoma volume, and the presence of blend sign on admission CT scan were associated with early hematoma growth (Table 3). The variables that were significant in the univariate logistic

**Table 2. Comparison of Baseline Demographic, Clinical, and Radiological Characteristics Between Patients With and Without CT Blend Sign**

Variables	Blend Sign Positive (n=29)	Blend Sign Negative (n=143)	P Value
Mean age, yr (SD)	60.21 (12.5)	60.45 (11.9)	0.925
Sex, male (%)	24 (82.8%)	93 (65.1%)	0.08
Alcohol consumption (%)	16 (55.2%)	63 (44.1%)	0.311
Smoking (%)	16 (55.2%)	62 (43.4%)	0.307
Hypertension (%)	17 (58.6%)	99 (69.2%)	0.283
Diabetes mellitus (%)	6 (20.7%)	17 (11.9%)	0.231
Time to baseline CT (SD)	2.34 (1.58)	2.39 (1.66)	0.897
Baseline hematoma volume (SD)	29.78 (22.28)	14.52 (11.35)	<0.001

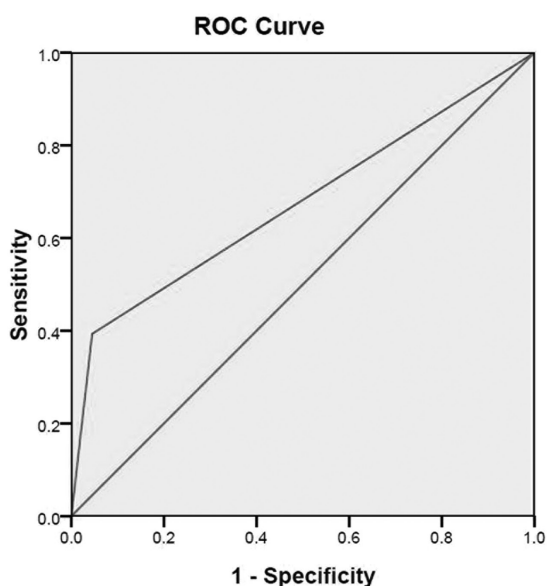
CT indicates computed tomography.

regression were retained in the multivariate logit model. The multivariate logistic regression analysis demonstrated that the time to baseline CT scan, initial hematoma volume, and presence of blend sign on baseline CT scan to be independent predictors of early hematoma growth (Table 4).

### Discussion

The dynamic hematoma growth is not uncommon in patients with ICH. In previous studies, absolute early hematoma growth has been observed in >70% of patients with ICH several hours after ictus.<sup>2,4</sup> Significant hematoma growth, which was defined as hematoma growth >33% or 12.5 mL has been reported in approximately one third of ICH patients.<sup>7,9-11</sup> Because early hematoma growth is associated with poor functional outcome, identification of potential predictors for hematoma growth is crucial for early diagnosis and management.

In our study, we have identified a novel and easy-to-use imaging marker for predicting hematoma growth. Blend sign was found in 16.9% of our patient cohort and showed excellent



Diagonal segments are produced by ties.

**Figure 2.** Receiver-operating characteristic (ROC) curve by using a binary definition of hematoma growth showed an area under the curve=0.674 and  $P<0.05$ .

**Table 3. Univariate Analysis of Predictors for Early Hematoma Growth**

Variable	Odds Ratio	95% Confidence Interval	P Value
Age	1.02	0.99–1.05	0.164
Sex	0.58	0.29–1.17	0.126
Current smoking	0.64	0.34–1.20	0.166
Alcohol consumption	1.01	0.54–1.88	0.992
Hypertension	0.8	0.41–1.58	0.527
Systolic blood pressure	1.01	0.99–1.02	0.153
Diastolic blood pressure	1.01	0.98–1.03	0.415
Diabetes mellitus	0.83	0.34–2.06	0.693
Intraventricular hemorrhage	0.79	0.40–1.55	0.48
Time to baseline CT	0.61	0.47–0.78	<0.001
Baseline ICH volume	1.06	1.03–1.09	<0.001
Blend sign on baseline CT	13.75	4.89–38.66	<0.001

ICH indicates intracerebral hemorrhage; and CT, computed tomography.



**Table 4. Multivariate Analysis of Predictors for Early Hematoma Growth**

Variable	Odds Ratio	95% Confidence Interval	P Value
Time to baseline CT	0.46	0.32–0.66	<0.001
Baseline hematoma volume	1.06	1.02–1.09	<0.001
Blend sign on baseline CT	20.23	5.13–79.77	<0.001

CT indicates computed tomography.

interobserver agreement between the readers. We have demonstrated that hematomas with blend sign on baseline CT scan are larger in size and more likely to expand than those without the sign. These imaging features are consistent with the natural history of the growing hematoma and may reflect active bleeding. Heterogeneity of hematoma has been recognized as an imaging predictor for hematoma growth.<sup>12</sup> The blend sign on nonenhanced CT is composed of blood with mixed CT densities and is a good indicator of hematoma heterogeneity.

The heterogeneity of hematoma has been investigated since early 1980s in patients with epidural hematoma.<sup>13,14</sup> Mixed-density hematoma has been observed in patients with epidural hemorrhage and is reported to correlate with active bleeding.<sup>15</sup> The hypointense area encapsulated within the hyperintense hematoma is termed the swirl sign and is found in a significant proportion of patients with epidural hematomas.<sup>16</sup> In previous studies, the association between the swirl sign and active bleeding has been validated in surgical exploration of patients with epidural hemorrhage. In a study of 13 patients with mixed-density subdural and epidural hematomas, Greenberg et al<sup>15</sup> found that 11 patients had active bleeding at the time of surgical decompression performed several hours after injury. In another study of 109 patients with epidural hematomas, Pruthi et al<sup>17</sup> reported that the mortality rate was significantly higher in patients with heterogeneous hematoma than those with homogenous hematoma. The authors also found that the mean hematoma volume was significantly larger in the mixed-density group than the homogenous hematoma group. These findings suggest that the hematoma heterogeneity was also associated with large hematoma volume. In a recent study, Kim et al<sup>18</sup> have assessed the use of the swirl sign in predicting hematoma growth in patients with ICH. They found that the CT swirl sign was not independently predictive of hematoma growth.

The novel CT blend sign may reflect blood of different age. The CT attenuation of blood is dependent on the time course of the bleeding.<sup>19</sup> The density of hematoma is affected by the individual components of the hematoma. The hemoglobin is the most important factor determining CT attenuation of the hematoma. Other components of the hematoma may have minimal impact on the attenuation values in the CT scan.<sup>20</sup> The CT appearance of hematoma becomes hyperattenuating as the blood becomes clotted.<sup>21</sup> An actively bleeding epidural hematoma may seem relatively hypoattenuating at nonenhanced CT than hematomas with clot retraction. We propose that the blend sign occurs because of liquid blood secondary to the presence of active bleeding. In our study, we have tried to use a quantitative definition of the blend sign, but failed to find an optimal Hounsfield unit range for each region. However, an 18 Hounsfield unit difference between the 2 density regions

may help identifying mixed-density hematomas that are at high risk for early hematoma growth. The blood of different age may mix together resulting in heterogeneous appearance of the blend sign. This might explain that CT blend sign may be used as predictor for hematoma growth.

In recent years, novel imaging predictors have been developed for early hematoma growth. The presence of contrast extravasation on CTA source images has been identified as a promising imaging predictor for hematoma growth. The CTA spot sign are usually multiple, round foci that present at the margin of hematoma. Recently, the reliability of the sign as an independent predictor for hematoma growth and has been validated in several prospective studies.<sup>8,9,22</sup> According to the Predicting Haematoma Growth and Outcome in Intracerebral Haemorrhage Using Contrast Bolus CT (PREDICT) study, the sensitivity, specificity, positive and negative predictive value of the CTA spot sign for predicting hematoma growth were 51%, 85%, 61%, and 78%, respectively.<sup>23</sup> In our study, the reported sensitivity, specificity, positive and negative predictive values of blend sign for predicting hematoma growth were 39.3%, 95.5%, 82.7% and 74.1%, respectively. Although the reported sensitivity of the CT blend sign is lower than the CTA spot sign, the CT blend sign is highly specific for predicting hematoma growth.

There are several limitations in the study. A limitation of our study is that only patients with 2 scans in the initial 6 hours of admission were studied which may lead to potential selection bias. We did not include an analysis of the CTA spot sign because early CTA examination was not routinely performed in our institution in patients with ICH. Future studies that incorporate CTA spot sign are needed to further clarify the association between CTA spot sign and the CT blend sign in patients with ICH.

In conclusion, our study has reported a novel and easy to use CT blend sign that predicts early hematoma growth in patients with ICH. The CT blend sign could be easily identified on regular nonenhanced CT and is highly specific for predicting hematoma growth. The CT blend sign may be used as an alternative method in institutions for prediction of hematoma growth where immediate CTA examination is not available.

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### Disclosures

None.

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