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Leakage Sign for Primary Intracerebral Hemorrhage

A Novel Predictor of Hematoma Growth

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Background and Purpose—Recent studies of intracerebral hemorrhage treatments have highlighted the need to identify reliable predictors of hematoma expansion. Several studies have suggested that the spot sign on computed tomographic angiography (CTA) is a sensitive radiological predictor of hematoma expansion in the acute phase. However, the spot sign has low sensitivity for hematoma expansion. In this study, we evaluated the usefulness of a novel predictive method, called the leakage sign.

Methods—We performed CTA for 80 consecutive patients presenting with spontaneous intracerebral hemorrhage. Two scans were completed: CTA phase and delayed phase (5 minutes after the CTA phase). By comparing the CTA phase images, we set a region of interest with a 10-mm diameter and calculated the Hounsfield units. We defined a positive leakage sign as a >10% increase in Hounsfield units in the region of interest. Additionally, hematoma expansion was determined on plain computed tomography at 24 hours in patients who did not undergo emergent surgery.

Results—Positive spot signs and leakage signs were present in 18 (22%) patients and 35 (43%) patients, respectively. The leakage sign had higher sensitivity (93.3%) and specificity (88.9%) for hematoma expansion than the spot sign. The leakage sign, but not the spot sign, was significantly related with poor outcomes (severely disabled, vegetative state, and death) in all of the patients (P=0.03) and in patients with a hemorrhage in the putamen (P=0.0016).

Conclusions—The results indicate that the leakage sign is a useful and sensitive method to predict hematoma expansion. **(*Stroke*. 2016;47:958-963. DOI: 10.1161/STROKEAHA.115.011578.)**

Key Words: hematoma ■ hematoma expansion ■ intracerebral hemorrhage ■ leakage sign ■ spot sign

Intracerebral hemorrhage (ICH) is a devastating disease with higher rates of mortality and morbidity than those of ischemic stroke.[1–3] Expansion of ICH, which occurs in ≤40% of patients with ICH, has been identified as one of the most important determinants of early neurological deterioration and poor clinical outcomes in primary ICH.[4] However, a method to reliably identify patients at risk of poor outcomes is lacking. Several retrospective studies have suggested that contrast extravasation on computed tomographic angiography (CTA), called the spot sign, might serve as a crucial predictor of hematoma expansion and mortality.[5–8]

A recent study evaluating the accuracy of the spot sign for predicting hematoma expansion reported a sensitivity of 53% (95% confidence interval, 49% to 57%) and specificity of 88% (95% confidence interval, 86% to 89%) based on findings in the arterial phase of CTA.[9] Because of the low sensitivity, a modified spot sign has been described, with consistent evolution in sites of active extravasation using dynamic CTA with an acquisition protocol involving a longer imaging time of >60 s.[1]

Aiming to find a more reliable method of predicting hematoma expansion, we established a new method called the leakage sign; after performing CTA, we performed another scan 5 minutes later and analyzed these 2 images (arterial phase and delayed phase). In this study, we analyzed the effectiveness of the leakage sign as a predictor of ICH expansion.

Materials and Methods

Patients and Treatment

All consecutive patients with primary ICH transferred to our institute between April 2012 and November 2013 were included. Because we performed CTA for all patients with ICH to determine whether any vascular lesions were present, patients for whom CTA could not be performed (eg, kidney dysfunction, restless moving) were excluded.

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Patients diagnosed with secondary ICH were also excluded; the causes of secondary ICH included trauma, aneurysm, vascular malformation, hemorrhagic infarction, venous infarction, Moyamoya disease, and brain tumor. Our institutional review board approved a prospective study of data for patients admitted through the emergency department or directly transferred for ICH during the study period.

Emergent craniotomy and hematoma evacuation were performed for patients with Glasgow Coma Scale (GCS) scores ≤8 points. However, emergent operations were not performed for patients whose family refused the operation or with the poorest neurological condition (GCS score of 3 points with bilateral dilated pupils).

Regardless of surgery, we aimed to control blood pressure at <140 mm Hg and performed the treatments according to the Japanese Guidelines for the Management of Stroke 2009.[10]

Clinical Data

The following patient clinical data were recorded at admission: age, sex, and mean arterial blood pressure. In addition, coagulation status at admission was evaluated using the international normalized ratio, prothrombin time, partial thromboplastin time, and modifying treatments, such as antiplatelet therapy, anticoagulation therapy, administration of fresh frozen plasma, vitamin K therapy, and platelet transfusion. Patients underwent a neurological examination at admission using the National Institutes of Health Stroke Scale and modified Rankin Scale; the latter was also completed at discharge.

Image Acquisition

Computed tomography (CT) acquisitions were performed according to the standard departmental protocols on 8-section General Electric helical CT scanners (BrightSpeed Edge; GE Healthcare, Milwaukee, WI). The first CT was performed for CTA (CTA phase), and the second scan (delayed-phase CT) was performed 5 minutes after the CTA (Figure 1). Plain CT was performed 24 hours after the first CT to evaluate the hematoma size and other intracranial findings.

Unenhanced, contiguous, axial, 5-mm-thick, plain CT images of the brain were obtained, from the vertex through the skull base, at 120 kVp and 320 mA. For the CTA, 70 mL ioversol (Optiray; Fuji Pharma Co, Ltd, Tokyo, Japan; 320 mg I/mL) was intravenously injected at a rate of 3 to 3.5 mL/s via a power injector through an intravenous line using the following parameters: 120 kVp; 240 mA; section thickness, 1.25 mm; section-acquisition interval, 1.25 mm; and pitch, 0.875:1. Adequate timing of the CTA acquisition was determined using the bolus tracking technique. Delayed-phase CT was performed using the same parameters as those for plain CT.

Detection of the Spot Sign and Leakage Sign

All plain CT scans were reviewed by 2 neuroradiologists who were blinded to the clinical interpretation of the images and the clinical condition of the patients. The initial and follow-up plain CT studies were evaluated at separate sessions; the images were anonymous and randomized so that the reviewer was blinded to the patient identity and the timing of the images (admission or follow-up). The images were evaluated for hemorrhage location and size, which was based on the section with the largest hemorrhage size (mm^2) of all the serial sections.

Radiological criteria for the spot sign were those reported previously[11,12]: at least 1 focus of contrast pooling within the ICH: high Hounsfield unit (HU) value (>120); discontinuous from normal or abnormal vasculature adjacent to the ICH; and any size and morphology.

The leakage sign was determined using the following procedure. Comparing the arterial and delayed-phase CT images, each reviewer set a region of interest (ROI) of 1-cm-diameter on the delayed-phase images; this region was considered the highest change in HU between the arterial and delayed CT images. Then, the reviewer set the same ROI circle on the arterial CT images at the same anatomic region. The HU values in the ROI were determined in each section of the arterial and delayed phase images, and a >10% increase in HU was considered a positive leakage sign, or hematoma expansion (Figure 1; Figure I in the online-only Data Supplement). Figure II in the online-only Data Supplement shows the differences in ROI placement, HU values, and final judgment of a positive leakage sign between Reviewers 1 and 2; there were no differences in any of these values.

Measurement of Changes in Hemorrhage Size

First, we chose the CT slice with the maximum hematoma area. When appropriate, the hematoma size was evaluated for multiple CT slices that showed hematomas of similar size (Figure IIIA and IIIB in the online-only Data Supplement). The CT scanner automatically plotted the pixel area with 50 to 80 HU, which corresponds with the hematoma value. To confirm if this plotted area was the same as the area of hematoma, we measured the number of pixels in the hematoma area 24 hours after onset; the same procedure was performed at the same anatomic slice, and the volume expansion was calculated (Figure

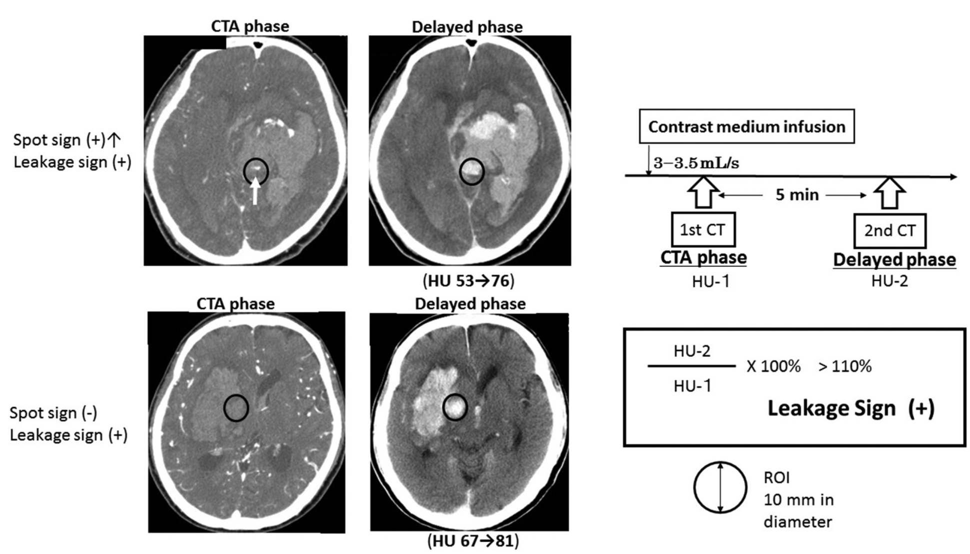

Figure 1. Diagnostic criteria for the leakage sign in patients with primary intracerebral hemorrhage. Based on the computed tomographic angiography (CTA) and delayed phase computed tomography (CT) images, a 1-cm-diameter region of interest (ROI) was set on the delayed phase images for the leakage of the contrast medium into the hematoma; the Hounsfield unit (HU) values in the ROI were determined in each section of the arterial and delayed phase images; and a >10% increase in HU was considered a positive leakage sign.

Table 1. Baseline Clinical and Radiological Characteristics of Patients With Primary Intracerebral Hemorrhage

Characteristic	Total (n=80)	Spot Sign (+), (n=18)	Leakage Sign (+), (n=35)
Age, y	67.9±12.9	67.5±11.9	68.4±12.9
Sex (male)	38 (47.5)	7 (38.8)	15 (42.8)
Blood pressure at admission, mm Hg			
Systolic	166.8±35.0	167.3±30.8	168.5±38.8
Diastolic	93.1±20.7	97.8±17.5	95.6±18.6
GCS at admission	9.41±4.03	8.5±3.97	8.4±3.79*
History of hypertension	47 (58.7)	13 (72.2)	22 (62.8)
Altered coagulation	4 (5.0)	1 (5.5)	1 (2.8)
Antiplatelet therapy	5 (6.2)	0 (0)	3 (8.5)
Laboratory data			
Platelet count at admission	15.8±6.6	17.6±6.56	16.4±6.45
INR at admission	1.12±0.42	1.12±0.33	1.07±0.253
aPTT at admission	27.81±5.06	28.07±5.4	26.8±5.01

aPTT indicates activated partial thromboplastin time (normal range, 25.0–36.0); GCS, Glasgow coma scale; and PT-INR, prothrombin time-international normalized ratio (normal value, 1.0).

*P=0.0015, for comparison between leakage sign (+) and leakage sign (-) groups. Values are reported as mean±standard deviation or n (%).

III in the online-only Data Supplement). As already described, we defined hematoma expansion as a >10% increase in hematoma size.

Statistical Analysis

Baseline demographics, hematoma volumes, and medication/medical history were compared between combinations of spot sign (+), spot sign (−), leakage sign (+), and leakage sign (−) and between the severe (GCS ≤8 points) and not severe (GCS ≥9 points) groups using Fisher exact tests, *t* tests, analysis of variance, or McNemar tests, as appropriate. The relationships between hematoma expansion and both spot and leakage signs were analyzed in patients who did not undergo surgery. Because hematoma growth could not be evaluated in the patients who underwent emergent evacuation of the hematoma at admission, we classified patients who underwent surgery or experienced an increase in the hematoma as the worsening course group (n=48) and the patients who did not undergo surgery or experience hematoma expansion as the no change in course group (n=32).

Table 2. Location of the Intracerebral Hemorrhage

Location	Total, n	Spot Sign (+) n	Spot Sign (+) %	Leakage Sign (+) n	Leakage Sign (+) %	*P* Value
Putamen	36	9	25.0	18	50.0	0.0027*
Thalamus	20	4	20.0	6	30.0	0.157
Subcortex	9	1	11.1	5	55.5	0.045†
Cerebellum	7	2	28.5	1	14.2	0.317
Brain stem	8	2	25.0	5	62.5	0.179

*P<0.01.
†P<0.05.

Statistical analyses were performed using the JMP version 11 software package (SAS Institute Inc Cary, NC).

Results

CTA was performed for the 80 consecutive patients with primary ICH. The mean patient age was 67.9 (range, 44–93) years, and the median GCS score at admission was 9.41 (range, 3–15) points.

There were no significant differences in the distributions of age, sex, history of hypertension, platelet count, and international normalized ratio between the spot sign–positive and leakage sign–positive patients (Table 1).

The spot sign was positive in 18 (22%) patients, and the leakage sign was positive in 35 (43%) patients (Table 1). All of the patients with a positive spot sign also had a positive leakage sign, except for 2 patients.

The ICH locations are shown in Table 2. The positive rates of the spot sign and leakage sign were significantly different between ICH located in the putamen and in the subcortex.

Figure IV in the online-only Data Supplement shows the mean HU values in the ROI for each group of patients. The HU values for the ROIs were statistically similar between the plain CT and CTA phase images (Figure IV and Table I in the online-only Data Supplement). The HU value significantly increased as time passed from the CTA phase to the delayed phase for the leakage sign (+)/spot sign (+) and leakage sign (+)/spot sign (−) groups.

Immediate hematoma evacuation was performed for 29 of the 80 (36%) patients. Ventricular drainage for hydrocephalus was performed for 10 of the 80 (8%) patients, and 41 (51%) patients were treated conservatively; of these 41 patients, surgery was declined by the families of 4 patients, and 7 patients had a GCS score of 3 points with bilateral dilated pupils. In the group of patients that did not undergo surgery, hematoma expansion was observed in 19 (24%) patients.

Of the entire patient group, poor outcomes (severely disabled or death) occurred in 50 (63%) patients at discharge, including 10 (13%) patients who died during hospitalization.

Relationships Between Hematoma Expansion and Predictive Signs of the Spot Sign and Leakage Sign on CT

In the analysis of the relationships between hematoma expansion and the spot and leakage signs in patients who did not undergo surgery (Figure 2), all of the patients with a maximum hematoma size <1000 mm^2 in any CT slice had better neurological symptoms (GCS score ≥9); unexpectedly, the presence of a hematoma <1000 mm^2 corresponded with surgical indication (Figure 2A).

Of the 7 patients with large hematomas (≥1000 mm^2) and hematoma expansion, 5 (71.4%) patients had a positive leakage sign; the patients with the poorest GCS score (3 points) had neither hematoma expansion nor a leakage sign/spot sign.

Of the patients with maximum hematoma sizes <1000 mm^2 at admission, 16 patients had hematoma expansion. Of these 16 patients, 11 (68%) had a positive leakage sign and 6 (37%) patients had a positive spot sign. Both signs were positive in 5 patients (Figure 2B).

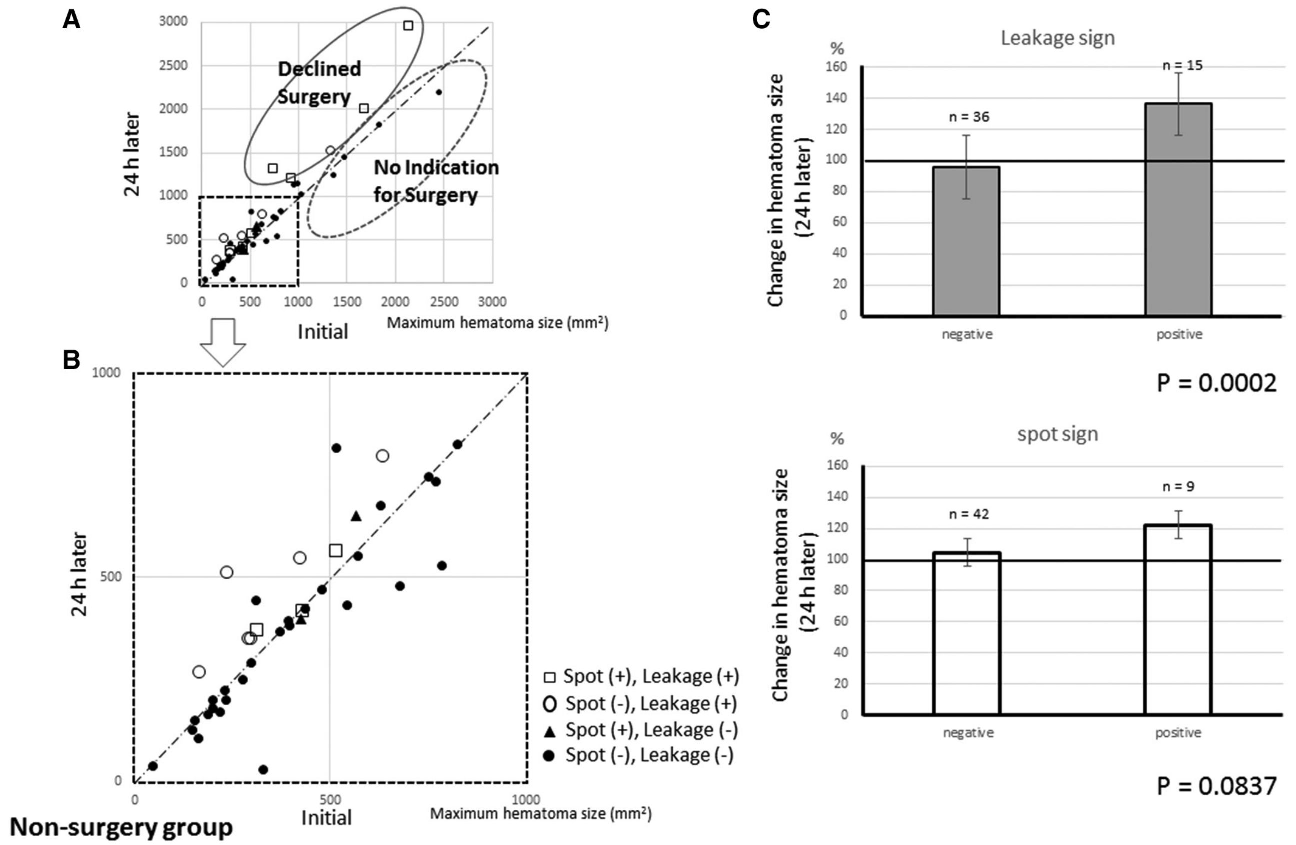

Figure 2. Relationship between the change in hematoma size and both predictive signs (leakage sign and spot sign). **A**, Dot blot analysis, with the *x* axis indicating the maximum hematoma size at admission and the *y* axis indicating the hematoma size 24 h later in the same slice of noncontrast computed tomography. **B**, Magnified plot analysis of the dotted squares from part **A**. **C**, Change in hematoma size during the 24-h period after admission, in the imaging studies for leakage sign (**C**, upper graph) and spot sign (**C**, lower graph).

Regarding hematoma expansion, patients with a positive leakage sign had significantly greater increases in the maximum hematoma size than patients with a negative leakage sign (136.2±8.09% versus 95.8±2.67%; *P*=0.002). There were no differences between patients with a positive spot sign and those with a negative spot sign (122.3±25.1% versus 104.5±4.35%; *P*=0.0837; Figure 2C).

In the patients requiring emergency hematoma evacuation, the spot sign was positive on the CT at admission in only 8 (27%) of the 29 patients who underwent the operation, and the leakage sign was positive in 19 (65%) of these patients (*P*=0.0081; data not shown).

In the worsening course group, a positive spot sign was present in 15 (31%) patients, and a positive leakage sign was present in 33 (68%) patients (*P*<0.001; Table II in the online-only Data Supplement). In the no change in course group, a positive spot sign was present in 3 (10%) patients, and a positive leakage sign was present in 2 (6%) patients; the difference in the proportion of patients was not significant.

The leakage sign had significantly higher sensitivity (93.3%) and specificity (88.9%) for hematoma expansion than the spot sign (Table 3). Furthermore, the combination of the leakage sign and spot sign showed the highest sensitivity (93.8%) and specificity (91.4.%), but these were not significantly different to those with just the leakage sign.

Contrast Extravasation and Clinical Outcomes

We analyzed the relationship between the outcomes, as assessed using the GCS scores, and the spot and leakage signs (Figure 3). The frequencies of the better outcomes (good recovery and moderately disabled) were significantly lower in patients with a positive leakage sign than in patients with a negative leakage sign (20.0% versus 51.5%; *P*=0.03) and in patients with a hemorrhage in the putamen and a positive leakage sign than in those with a hemorrhage in the putamen and a negative leakage sign (22.0% versus 64.7%; *P*=0.0016). There were no significant differences in the outcomes based on the spot sign.

Discussion

The findings of the present study indicate that the leakage sign is useful for predicting growth of a primary ICH, with good reproducibility, a clear definition, the convenience of

Table 3. Sensitivity and Specificity of Spot Sign and Leakage Sign to Predict Hematoma Expansion in This Prospective Study

	Sensitivity (95% CI)	Specificity (95% CI)
Spot sign	77.8% (0.485–0.934)	73.8% (0.675–0.772)
Leakage sign	93.3% (0.757–0.988)	88.9% (0.815–0.912)
Combination of spot and leakage sign	93.8% (0.7977–0.992)	91.4% (0.830–0.951)

CI indicates confidence interval.

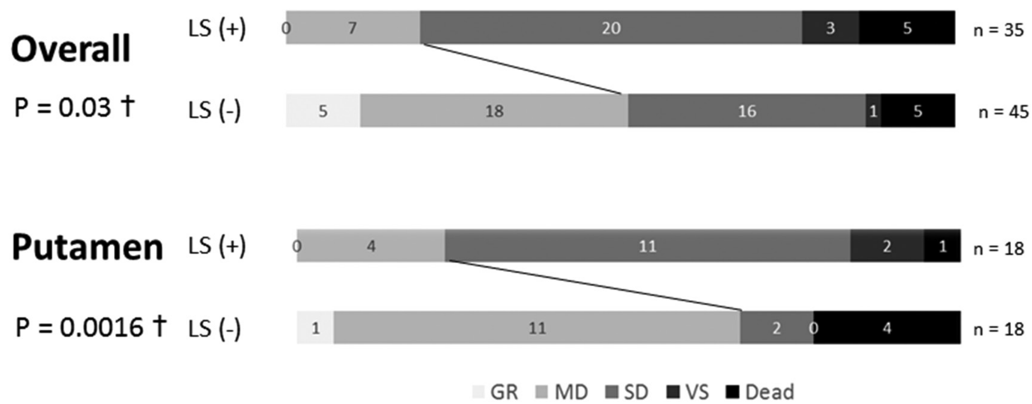

Figure 3. Outcome of all the patients with primary intracerebral hemorrhage (n=80) and those with a hemorrhage in the putamen (n=36).

waiting only 5 minutes, a restrictive ROI of a 1-cm diameter, and detection of a 10% increase in HU. Furthermore, the sensitivity (93.3%; 95% confidence interval, 0.757–0.988) and specificity (88.8%; 95% confidence interval, 0.815–0.912) for hematoma expansion were high, and the leakage sign can predict poor outcomes for all patients with a primary ICH and specifically those with an ICH in the putamen.

The spot sign is currently considered a useful radiological sign on CTA showing extravasation of contrast media or a bleeding artery in a hematoma and also as a prognostic predictor.[5,11] However, the spot sign reportedly indicates both active bleeding[13] and a striate artery.[14]

A modified spot sign has been described recently, in which delayed-phase CT was performed 2 to 5 minutes after the first CT.[6,15,16] The sensitivity and specificity were higher with the evaluation of the delayed-phase CT. However, these studies did not report the specific time of the second CT or the definition of a positive finding.

In the present study, we intended to identify more subtle extravasation than could be accomplished using the spot sign, resulting in the choice of waiting 5 minutes after the CTA for the delayed-phase CT. Furthermore, we defined a positive finding as a 1-cm diameter ROI and a >10% increase in HU in the ROI, resulting in a method that is easy to perform and can be completed in all institutes with a CT scanner.

With the leakage sign, it is easy to understand why extravasation can be identified when it could not be confirmed in the arterial phase of CT. During the 5-minute period, extravasation of the contrast medium became clearer than with the CTA phase image. Although it could be argued that 5 minutes is not enough time to detect extravasation, the risk is greater in unconscious patients with a longer wait.

In the present study, all of the patients were able to wait 5 minutes because they were without respiratory or cardiac problems. Because of the high specificity and sensitivity for hematoma expansion in the present study, we suggest that 5 minutes is an appropriate time period to delay the second CT.

Another potential issue is the greater radiation exposure with the present method because it requires an additional CT scan compared with the conventional method. However, if we can detect hematoma growth, the clinical benefit is greater than the risk of additional radiation, and additional unnecessary segmental scans could be avoided during hospitalization.

The effectiveness of surgical removal of a spontaneous ICH is controversial,[16,17] but the indication for surgery becomes more limited as time passes. In emergency care, the need for emergency surgery for cerebral hemorrhage is difficult to determine. For patients for whom surgery is not indicated, the most important issue is prevention of hematoma expansion.[4] Although aggressive therapy to reduce blood pressure and active craniotomy are controversial, these aggressive therapies might be useful for high-risk patients with a positive leakage sign because hematoma expansion is the most important factor for a poor outcome. Therefore, we think that the leakage sign is superior to the spot sign for predicting hematoma growth within several hours in patients with a critical hematoma size. Based on a previous review of studies regarding predictive methods for hematoma expansion using CTA and delayed CTA, such as the spot sign and modified spot sign,[9] the sensitivity and specificity of the current method were the highest. Despite some similarities between the leakage sign and some previous methods,[18,19] the details of these previous methods were not provided. Therefore, we consider that the leakage sign has good reproducibility and is easy to use.

In the present study, the presence or absence of the spot sign or leakage sign did not affect the operative indication. Using the leakage sign to predict hematoma growth could help to identify patients who require future evacuation of the hematoma in the early stage.

Conclusions

The leakage sign was more sensitive than the spot sign for predicting hematoma expansion in patients with ICH. In addition to the indication for an operation and aggressive treatment, we expect that this method will be helpful to understand the dynamics of ICH in clinical medicine.

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Disclosures

None.

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