Stroke

TOPICAL REVIEW

Spot Sign in Intracerebral Hemorrhage: Critical Reappraisal and Future Clinical Implications

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ABSTRACT: Hematoma expansion (HE) is a common occurrence affecting around 10% to 30% of patients with acute intracerebral hemorrhage within the initial hours from symptom onset and is the only modifiable factor associated with poor clinical outcomes. The detection of contrast extravasation on computed tomography (CT) angiography, known as the spot sign, was initially embraced as a promising radiological marker for predicting HE that could aid patient selection for acute interventions aimed at minimizing HE. However, the initial enthusiasm waned as clinical studies failed to show clear clinical benefits of hemostatic treatments when patients were selected based on the presence of this imaging marker. In this narrative review, we provide a comprehensive summary of the pathophysiology, definitions, imaging protocols, and predictive performance of the spot sign, along with the clinical studies that have selected and treated patients based on its presence. Finally, we delve into some nuances of the spot sign that can enhance its predictive performance and help stratify HE risk with greater precision. These features include static findings observed on single-phase CT angiography (ie, number, volume, CT density, and colocalization with hypodensities), as well as dynamic findings identified on multiphase/dynamic CT angiography (ie, timing of appearance, volume increase, volume decrease for tissue dispersion, and CT density changes). In this reappraisal of the spot sign, we aim to reinvigorate research on advanced neuroimaging in intracerebral hemorrhage that could lead to a more accurate HE prediction. This could facilitate better selection for therapies aimed at preventing HE or surgical approaches to address the bleeding source.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: angiography ■ cerebral hemorrhage ■ hematoma ■ hemorrhagic stroke ■ tomography

Intracerebral hemorrhage (ICH) is a devastating condition that occurs when a cerebral blood vessel leaks, resulting in bleeding into the brain parenchyma.[1] Although less common than ischemic stroke, it causes higher mortality and morbidity.[2] Hematoma expansion (HE) is a common occurrence affecting around 10% to 30% of patients with acute ICH within the initial hours from symptom onset and is the only modifiable factor associated with poor clinical outcomes.[3,4] Therefore, timely management to prevent or mitigate HE is an important treatment strategy and includes hemostatic treatment, intensive blood pressure control, anticoagulation reversal, and early surgical evacuation.[3,5] However, these treatments have often demonstrated limited benefits in clinical trials and are hampered by potential side effects.[6–10] Thus, accurately identifying patients at higher risk of experiencing significant HE could inform acute decision-making and prognostication in patients with ICH.[3]

Different noncontrast computed tomography (NCCT) markers have been proposed over the past decade to predict HE.[3,11,12] These markers provide some understanding of how the hematoma might have evolved in the minutes or hours preceding imaging acquisition, indicating that bleeding might have occurred at multiple

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time points (heterogeneous density) and in different locations (heterogeneous shape).[3,11,12] However, the use of computed tomography angiography (CTA) to detect contrast extravasation within the boundaries of the hematoma, known as the spot sign,[13,14] has consistently yielded superior accuracy for predicting HE occurrence and severity compared with NCCT markers when radiological features are considered independently.[15,16] Yet, the initial enthusiasm surrounding the spot sign and advanced neuroimaging in ICH[17,18] has progressively waned as subsequent trials failed to show clear clinical benefits of hemostatic treatment when patients were selected based on the presence of this imaging marker.[19–21]

In this reappraisal, we review the pathophysiology, definitions, and predictive performance of the spot sign. We critically reevaluate imaging-guided clinical trials that have used the presence of the spot sign as a criterion for patient selection. Moreover, we discuss potential strategies to enhance the predictive performance of the spot sign, including its integration into scores and a detailed analysis of the spot sign high-risk features and nuances. Finally, we discuss how refining imaging criteria related to the spot sign can inform patient selection, leading to more tailored management strategies and improved therapeutic outcomes.

SPOT SIGN PATHOPHYSIOLOGY, DEFINITIONS, AND MIMICS

The spot sign concept arises from a simple yet elegant idea: when contrast is injected into the blood of patients with active and ongoing bleeding, it is likely to extravasate into the bleeding site from the source bleeding arteriole or peripheral small vessels. Contrast extravasation was initially described in anecdotal ICH cases during imaging with cerebral angiography or intrahematoma gadolinium-enhanced magnetic resonance imaging (MRI).[22–24] Subsequently, in 2007, Wada et al[13] and Goldstein et al[25] independently introduced the concept of the CTA spot sign. Wada et al[13] defined the spot sign as any visual detection of 1 or more 1 to 2 mm foci of enhancement within the hematoma on CTA source images, revealing a strong association between the spot sign and HE, as well as worse clinical outcomes.[13] Goldstein et al[25] defined contrast extravasation as the presence of any high-density material within the hematoma on CTA source images.[25]

The predictive performance of the spot sign for HE was later validated in a large, multicenter, prospective study called PREDICT (Predicting Hematoma Growth and Outcome in Intracerebral Hemorrhage Using Contrast Bolus CT).[14] Subsequent studies have confirmed the robustness of the spot sign as a predictor of HE also in infratentorial locations, including cerebellar and pontine ICH.[26,27] Interestingly, contrast prominence and extravasation were more frequently present in primary intraventricular hematoma but not associated with expansion.[28] This disparity may stem from variations in microvessel compositions within the ventricles, especially in the choroid plexus, a highly organized tissue that lines most of the ventricles and has a high permeability due to cerebrospinal fluid production.[29] This can result in an increased susceptibility to leakage but also effective hemostasis, leading to a higher proportion of false positives. Alternatively, the blood within the ventricles might be washed out by the physiological circulation of cerebrospinal fluid from the ventricles to the subarachnoid spaces, leading to an underestimation of HE. In summary, the spot sign emerged as the most significant radiological marker for HE for supratentorial and infratentorial intraparenchymal hematoma.

In the PREDICT study, 4 radiological criteria were provided to define the spot sign: (1) a serpiginous or spot-like appearance within the margin of a parenchymal hematoma without connection to an outside vessel, (2) a maximum diameter >1.5 mm, (3) a contrast density at least twice that of the background hematoma, and (4) no hyperdensity at the corresponding location on NCCT (to exclude calcium mimics).[30] Slightly different definitions have been used over the years. A recent meta-analysis compared the predictive accuracy of the spot sign definitions and revealed the best accuracy for HE when both discontinuities from the normal or abnormal vasculature adjacent to the hematoma and an attenuation rate ≥120 Hounsfield unit are applied.[14,31] These criteria are meant to maximize discrimination from spot mimics, which include intracranial calcifications, neoplasms, microaneurysms, and small arteriovenous malformations.[32,33] Another potential pitfall of the spot sign is that it may represent a site of arrested microbleeding where the leakage rate is decreasing due to endogenous hemostatic pathways,[34] especially when detected beyond the initial hours after symptom onset. This finding is consistent with the significant correlation between onset-to-imaging time and predictive performance of the spot sign.[35]

CTA SPOT SIGN PREVALENCE, INTERRATER AGREEMENT, AND PREDICTIVE PERFORMANCE FOR HE

Different populations, computed tomography (CT) imaging protocols, criteria to define spot signs, and timing of acquisition among studies resulted in heterogeneous findings regarding the prevalence and predictive performance of the spot sign.[31,36,37] A meta-analysis of 5087 patients revealed a prevalence of 23%, pooled positive predictive value of 0.60, and sensitivity of 0.57 for predicting HE.[15] These results were in line with 2 other meta-analyses.[38,39]

However, mounting evidence supports an increase in predictive performance when earlier time from onset, higher density, and spatial evolution features (change in size) of the spot signs are evaluated, especially when incorporated into a score.[40–43] A multicenter analysis demonstrated a moderate interrater agreement (κ=0.60) and a median time needed to assess the spot sign of 2 minutes.[44] Yet, a more recent study showed an excellent interrater agreement (κ=0.93).[45]

It is important to note that the standard definition of HE (≥33% or ≥6 mL) represents an arbitrary oversimplification of a severity spectrum, and the predictive performance of the spot sign with other definitions and more granular categorizations has been underinvestigated. Notably, in 1 study, the spot sign was the individual radiological marker with the highest positive predictive value (0.51) for severe HE (≥66% or ≥12.5 mL).[16]

CTA SPOT SIGN IN ANTIHEMATOMA EXPANSION CLINICAL TRIALS

As the spot sign emerged as the most predictive radiological marker of HE, several clinical trials have adopted an imaging-selection strategy focused on its presence to select only patients at elevated risk of HE. The hallmarks of anti-HE therapy include hemostatic treatments, intensive blood pressure control, anticoagulation reversal, and early surgical evacuation. Here, we review these treatment approaches with a particular focus on the role of the spot sign in some of these trials.

Hemostatic Treatments

Hemostatic treatments, such as rFVIIa (recombinant factor VIIa) and tranexamic acid (TXA), have shown some statistically significant benefits in radiological outcomes by reducing the HE, yet inconsistent or no improvements in functional outcome.[46–48] However, the anticipated clinical effect of anti-HE drugs is small because only 20% to 25% of patients experience substantial HE.[4] As a result, most patients may benefit marginally from hemostatic treatment.[3] To increase the likelihood of demonstrating a clinical benefit of hemostatic treatment, researchers likely needed to substantially increase their sample sizes or select patients at higher risk of experiencing HE. However, it is important to note that those at the highest risk of HE, with a more severe natural history, may ultimately have a reduced chance of benefitting from any interventions. The 2 most promising selection criteria were a shorter time window from symptom onset to hemostatic treatment and the presence of CT or CTA markers of HE. Drawing parallels with hyperacute ischemic stroke treatments,[49] the imaging-guided selection was preferred over early time presentation in subsequent clinical trials of ICH.

Specifically, 4 clinical trials have selected patients based on the presence of the spot sign to increase the likelihood of demonstrating the benefit of hemostatic treatments: SPOTLIGHT (Spot Sign Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy)/STOP-IT (The Spot Sign for Predicting and Treating ICH Growth Study) (published together), STOP-AUST (Spot Sign and Tranexamic Acid on Preventing ICH Growth–Australasia Trial), and TRAIGE (Tranexemic acid for acute intracerebral haemorrhage growth based on imaging assessment) (Table 1).[19–21] These trials investigated the use of rFVIIa and TXA in small-moderate spontaneous ICH within 4.5 to 6.5 hours from symptom onset. All 4 trials found no significant clinical or radiological benefits. These results might have been attributed to several factors: (1) a relatively small number of patients, (2) a long median time from onset to drug administration, and (3) unexpectedly low absolute HE in participants. Moreover, a prespecified analysis of SPOTLIGHT showed that in most patients, the majority of HE had already been completed in the short time interval between baseline imaging acquisition and

Table 1. Spot Sign–Guided Selection Trials

	Design and size	Intervention	Main inclusion criteria	Time metrics in treatment arm	Main findings
SPOTLIGHT+STOP-IT (2019)*	Randomized, placebo-controlled, phase II trial (n=69)	rFVIIa (80 µg/kg) vs placebo	Within 6.5 h from onset	Onset to drug, 195 (IQR, 157–266) min	No significant difference in hematoma expansion or 3-mo functional outcome
			ICH volume <90 mL	CT to drug, 79 (IQR, 61–99) min	
STOP-AUST (2020)	Randomized, placebo-controlled phase II trial (n=100)	Tranexamic acid (1 g over 10 min+1 g over 8 h) vs placebo	Within 4.5 h from onset	Onset to drug, 153 (IQR, 114–215) min	No significant difference in hematoma expansion or 3-mo functional outcome
			ICH volume <70 mL	CT to drug 40 (IQR, 29–55) min	
TRAIGE (2021)†	Randomized, placebo-controlled phase II trial (n=171)	Tranexamic acid (1 g over 10 min+1 g over 8 h) vs placebo	Within 6 h	Onset to drug 290 (IQR, 205–369) min	No significant difference in hematoma expansion or 3-mo functional outcome
			ICH volume <70 mL	CT to drug 128 (IQR, 67–172) min	

CT indicates computed tomography; ICH, intracerebral hemorrhage; IQR, interquartile range; rFVIIa, recombinant factor VIIa; SPOTLIGHT, Spot Sign Selection of Intracerebral Hemorrhage to Guide Hemostatic Therapy; STOP-AUST, Spot Sign and Tranexamic Acid on Preventing ICH Growth–Australasia Trial; STOP-IT, The Spot Sign for Predicting and Treating ICH Growth Study; and TRAIGE, Tranexamic Acid for Acute Intracerebral Hemorrhage Growth Based on Imaging Assessment.

*SPOTLIGHT and STOP-IT were 2 independent studies with harmonized protocols and preplanned individual patient-level pooled analysis.

†In total, 45% of patients were enrolled based on the presence of the blend sign or black hole sign.

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drug administration—confirmed by an immediate post-dose NCCT—hampering any potential treatment benefit of hemostatic therapy in that trial population.[50]

Similarly, post hoc analyses of trials that were not imaging-guided in the selection of patients also failed to demonstrate an interaction between the hemostatic therapeutic effect and the spot sign. A secondary analysis of the TICH-2 trial (Tranexamic Acid for Hyperacute Primary Intracerebral Hemorrhage) did not reveal any additional benefit of TXA over placebo in the subgroup of patients with positive spot sign.[51] However, TXA was administered after a median of 225 minutes from symptom onset, and the median delay between imaging acquisition and drug administration was 76 minutes, thereby minimizing any potential hemostatic benefit.

A recent individual patient meta-analysis of spot sign–positive patients from clinical trials, however, did show a modest reduction of hematoma growth of 1.6 mL with TXA administered within 4.5 hours of symptom onset.[52]

The relationship between timing and spot sign can further hint at the failure of these trials, as the positive predictive value of the spot sign progressively decreases as time elapses.[35] Currently, RCTs have switched focus to selecting patients in an ultraearly time window (<2 hours) for all participants rather than based on imaging features such as the spot sign.[53,54]

Intensive Blood Pressure–Lowering Interventions

Intensive blood pressure–lowering interventions and bundle care strategies have demonstrated radiological and clinical benefits more consistently,[55,56] especially in the early time window.[6,8] Although no imaging-guided trial has been conducted, a subanalysis of the ATACH-2 trial (Antihypertensive Treatment of Acute Cerebral Hemorrhage) did not demonstrate that patients with spot signs specifically benefit from intensive blood pressure intervention.[57] However, the sample size was relatively small (133 patients) and, therefore, likely underpowered to show an association. Moreover, the CTA was not performed immediately after baseline NCCT but over an hour later, on average, when the predictive ability of the spot sign degrades, and HE might have already occurred.[35]

Anticoagulation Reversal

Several clinical trials have explored the safety and efficacy of anticoagulation reversal, including prothrombin complex concentrate, andexanet, and idarucizumab, in ICH associated with anticoagulation.[5,10,56,58,59] These treatments showed laboratory and radiological benefits but no long-term functional outcome improvement. Yet, no patient selection based on spot signs or subanalyses to explore treatment interactions of anticoagulant drug reversal with the spot sign has been performed to date.

Early Surgical Evacuation

Early minimally invasive surgery demonstrated clinical benefits in post hoc analyses of the MISTIE III trial (Minimally Invasive Surgery With Thrombolysis in Intracerebral Hemorrhage Evacuation), particularly in patients who achieved residual clot volume <15 mL.[60] Notably, minimally invasive surgery is the only intervention, apart from the care bundle protocol investigated in INTERACT3 (The Third Intensive Care Bundle With Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial),[56] that has met the primary functional end point in a randomized clinical trial for ICH, as demonstrated in the recent ENRICH trial (Early Minimally Invasive Removal of Intracerebral Hemorrhage).[61] Although no selection criteria based on spot signs or subanalyses have been conducted to explore treatment interactions between early surgery and spot signs, some surgical trials have specifically excluded patients with spot signs.[62] Indeed, spot sign is associated with more intraoperative and postoperative bleeding, resulting in larger residual volumes posthematoma evacuation.[63,64] However, the spot sign may also help to optimize the surgical approach as it can provide insights into the site of intraoperative active bleeding during endoscopic surgery. Electrocoagulation at that site might be important for minimizing bleeding—targeted surgical hemostasis.[64] Therefore, the spot sign may be useful in tailoring specific surgical interventions in future trials. Noteworthy, early surgical evacuation not only addresses HE but also reduces secondary injury by removing a substantial portion of the initial hematoma.[62]

CTA SPOT SIGN SCORES

To improve our ability to select patients with the highest risk of developing HE for clinical trials, we can evaluate the high-risk features and nuances of the spot sign or we can integrate the spot sign with other clinical and radiological risk factors into predictive scores.

In the last 15 years, multiple predictive scores for HE have been developed, incorporating clinical, laboratory, and radiological features.[3,65] Among these, 7 scores have integrated the spot sign and are summarized in Table 2. These scores consistently outperformed those based solely on NCCT markers, showing C statistics ranging from 0.68 to 0.93.[50,65–68,70] The spot sign score, the only one that integrates high-risk features of the spot sign rather than simply focusing on its presence or absence, demonstrated the best predictive performance: C statistic >0.8 in the validation cohort.[42]

Notably, none of these scores were used to guide the selection of patients for anti-HE treatments, nor were they explored in secondary analyses of these trials. Therefore, HE scores are not currently used for clinical practice decision-making.

Table 2. Hematoma Expansion Prediction Scores With Spot Sign

CTA scores	Score assessment	C statistic in development cohorts	C statistic in validation cohort
sCTA or mCTA spot sign score (maximum score=4); Delgado Almandoz et al[66]	Spot signs number=1–2 (1 point); ≥3 (2 points)	0.93	0.68–0.93
	Spot sign maximum axial diameter ≥5 mm=1		
	Spot sign maximum CT density ≥180 HU=1		
9-point score (maximum score=9); Brouwers et al[67]	Warfarin use=2	0.72	0.71–0.77
	Onset-to-imaging time <6 h=2		
	Initial ICH volume=30–60 mL (1 point); >60 mL (2 points)		
	Spot sign present=3		
PREDICT A score (maximum score=21); Huynh et al[68]	Onset-to-imaging time=for each hour 5–0	0.78–0.86	No validation
	Warfarin use=6		
	Spot sign number=1 (4 points); ≥2 (8 points)		
	GCS score ≤13=4 points		
PREDICT B score (maximum score=28); Huynh et al[68]	Onset-to-imaging time=for each hour 5–0	0.77–0.84	No validation
	Warfarin use=6		
	Spot sign number=1 (4 points); ≥2 (8 points)		
	NIHSS score=5–14 (4 points); ≥15 (7 points)		
Acute ICH growth score (maximum score=7); Al-Ajlan et al (ISC abstract)[69]	Ultraearly growth >5 mL/h=1	0.76	No validation
	Irregular shape=1		
	Heterogeneous density=1		
	Fluid-level sign=1		
	Spot sign=1		
	Anticoagulation use=2		
sCTA expansion score (maximum score=3); Rodriguez-Luna et al[70]	Ultraearly growth >5 mL/h=1	0.75	0.72
	Spot sign=2		
mCTA expansion score (maximum score=2); Rodriguez-Luna et al[70]	Spot sign in first phase=1 point	0.79	0.73
	Spot sign in any phase=1 point		

CT indicates computed tomography; GCS, Glasgow Coma Scale; HU, Hounsfield unit; ICH, intracerebral hematoma; mCTA, multiphase CT angiography; NIHSS, National Institutes of Health Stroke Scale; PREDICT, Predicting Hematoma Growth and Outcome in Intracerebral Hemorrhage Using Contrast Bolus CT; and sCTA, single-phase CT angiography.

CTA SPOT SIGN HIGH-RISK FEATURES

The spot sign has been historically considered a binary variable, present or absent. Yet, a more nuanced assessment, considering certain recently described high-risk features, may help refine its predictive performance (Figure 1). Broadly, we can categorize these features as static or dynamic, depending on whether they can be evaluated on a single-phase or multiphase/dynamic CTA imaging protocol. These static and dynamic features of the spot sign might allow for a more granular stratification of HE occurrence and severity risk. Table 3 provides a summary of recommended definitions and imaging protocols for spot sign features, which are further discussed in detail in the text below.

Static High-Risk Features (Single Snapshot Imaging)

Single-phase CTA allows for capturing static spot sign features, which comprise (1) morphological features, (2) location characteristics, and (3) interaction with surrounding tissues.

Morphological features associated with an increased risk of HE reflect the spot sign burden and include a greater maximum axial diameter, higher maximum CT attenuation, and the number of spot signs.[66] Specifically, the latter has been observed as the most critical feature in predicting HE.[43] The simultaneous presence of multiple spot signs observed in some patients might support the hypothesis that HE is driven by the rupture of adjacent small vessels around the initial ICH due to mechanical tearing by the growing mass—the avalanche model, first described by Fisher.[71] Alternatively, multiple spot signs could still originate from a single bleeding site, with the contrast spreading briskly to areas of least resistance—the single source/simplest bleeding location model as illustrated in the ongoing bleeding in acute ICH video published in *Lancet*.[3,72] A higher CT density of the spot sign has been associated with an increased HE risk.[66,73–75] Noteworthy, dual-energy CT scans can effectively differentiate between hyperdense iodine extravasation and blood.[75,76] In some cases, the hyperdensity of the hematoma might interfere with detecting the low contrast extravasation in single-phase CTA. Therefore,

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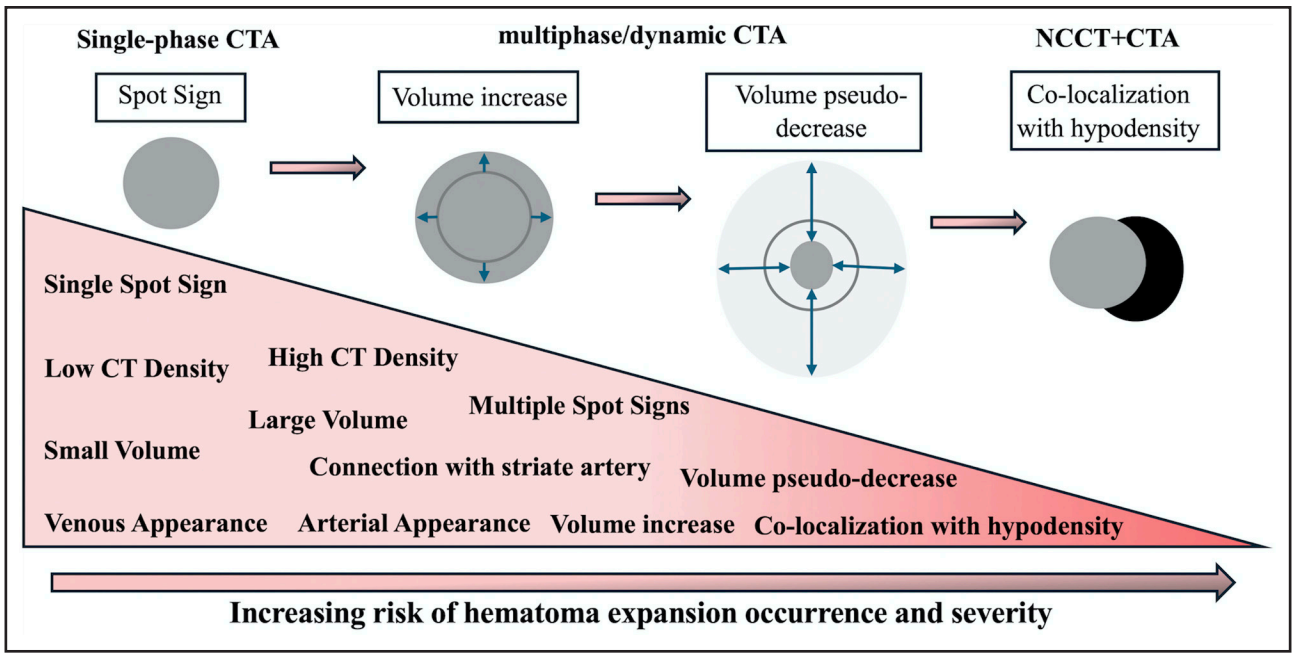

Figure 1. Hematoma expansion risk stratification based on static and dynamic features of the spot sign.
Illustration of spot sign features that progressively increase in risk for hematoma expansion occurrence and severity. The gray circle represents the spot sign, while the blue arrows represent its dynamic changes, indicating volume increase or pseudodecrease in case the contrast expansion dilutes with the surrounding hematoma (light gray area). The black circle represents a noncontrast computed tomography (NCCT) hypodensity sign. Some of these features have been previously addressed with specific names, such as computed tomography (CT) density (ie, iodine sign), volume modifications over time (ie, extravasation rate, leakage rate), connection with the striate artery (ie, spot and tail sign), and colocalization with hypodensity (ie, Black-&-White sign). CTA indicates CT angiography.

dual-energy CT scans can improve the sensitivity of the spot sign for HE with a minimal trade-off in specificity.[76] The spot sign identified with this methodology is also called the iodine sign. [76]

The spot sign can present in various shapes, including round, ovular, multinodular, serpiginous, or irregular, yet no association between specific shapes and HE risk has emerged. Moreover, the location characteristics of the spot sign, such as its central or peripheral position within the hematoma volume, as well as whether it is located in a lobar or deep brain region, do not seem to influence the risk of HE.[77]

The interaction of the spot sign with the surrounding vascular and nonvascular structures can also play a crucial role. In supratentorial ICH, the connection between the spot sign and an intrahematoma striate artery (called the spot and tail sign) was identified in 50% of patients with a positive spot sign and was an independent predictor of acute neurological deterioration.[78] One possible explanation for this finding is that the continuous blood supply through the striate artery to the rupture site more likely reflects active bleeding compared with the spot sign with no associated enhanced vessel.

The colocalization of NCCT hypodensities and the spot sign (called the Black-&-White sign) has been observed in about one-third of spot sign–positive patients (Figure 2).[79] This sign showed a 100% positive predictive value for HE in a single-center development cohort, while in a multicenter validation cohort, it showed a 79% positive predictive value.[80] From a pathophysiological perspective, the Black-&-White sign arguably represents a site of immature hemostasis (hypodensity) and ongoing bleeding (spot sign), reflecting a site of very active bleeding.

Dynamic High-Risk Features (Multiple Snapshot/Dynamic Imaging)

The acquisition of 2 or more images after the injection of contrast allows for capturing dynamic spot sign features, including (1) the time of first appearance and (2) the volume and density evolution. As a rule of thumb, the longer we observe the hematoma after contrast injection, and the more images we collect, the better we can capture the dynamic nature of the spot sign. However, factors such as radiation exposure, cost, and time must be carefully balanced. Multiple neuroimaging protocols have been adopted to explore the dynamics of the spot sign in ICH, including multiphase CTA,[41,81,82] delayed CTA,[34,83–89] CT perfusion,[90–92] and postcontrast CT.[93] Despite variations in the number of images acquired and duration from contrast injection to last image acquisition (ranging from 30 to 300 s), all these protocols consistently demonstrated improved predictive performance of the spot sign for HE.[40,93]

The time of the first appearance of the spot sign is directly correlated with the risk of HE: the earlier the spot sign appears, the greater the risk.[41,81,86,94] However, a longer

Table 3. Recommended Definitions and Imaging Protocols of Spot Sign

	Definitions	Imaging protocol to optimize
Spot sign	A spot-like appearance (1) within the margin of a parenchymal hematoma without connection to an outside vessel, (2) a maximum diameter >1.5 mm, (3) a contrast density at least double that of the background hematoma or ≥120 HU, and (4) no hyperdensity at the corresponding location on NCCT	Single-phase CTA Tube voltage 100–120 kV and current 100–750 mA
Spot and tail sign	A linear contrast enhancement originating from the M1 segment of the middle cerebral artery (corresponding to a striate artery) connected to a spot sign	Single-phase CTA Coronal multiplanar reconstruction with 3 mm thick images
Iodine sign	A spot-like appearance with an internal focus iodine concentration >7.82 (100 µg/mL)	Dual-energy CT Iodine-based material decomposition images
Black-&-White sign	Any visually assessed CTA spot sign localized within or adjacent to a hypodensity sign on the corresponding NCCT	NCCT+single-phase CTA Immediate CTA (performed within 10–15 min from NCCT without moving the patient's head)
Venous-phase spot sign	A spot sign first appearing in the venous filling phase of CTA	At least 1 delayed CT image acquisition between 30 and 300 s from the first acquired image: Multiphase CTA: 2 images acquired at ≈15 and 30 s from the first image. Dynamic CTA/CT perfusion: multiple images acquired for 60–90 s. Postcontrast CT: 1 image acquired between 60 and 300 s after contrast injection.
Positive and negative leakage rate in the spot sign	Any visually assessed spot sign clear changes at 2 different time points in terms of either increase (positive) or decrease (negative) volume.	

CT indicates computed tomography; CTA, CT angiography; HU, Hounsfield unit; and NCCT, noncontrast CT.

observation duration after contrast injection enhances the sensitivity of the spot sign by detecting contrast extravasation that may occur during the venous filling phase or even later.[41] The delayed appearance of the spot sign might be linked to a low ejection fraction, elevated peripheral vascular resistance, or elevated intracranial pressure that produces a tamponade effect. Alternatively, a late/venous-phase presentation could suggest lower flow bleeding, while an early/arterial phase presentation might indicate higher flow bleeding.

The evolution of the spot sign could be even more informative than the time of first appearance (Figure 3). First, it might improve the discrimination of spot mimics: a spot sign that does not change over time is unlikely to be an actual site of active bleeding.[33,34] This is especially important for late presentation when the spot sign is more likely to be a site of arrested bleeding rather than ongoing bleeding.[35] Second, spot sign volume increase, called extravasation rate[84] or positive leakage rate, [82] was consistently correlated with a significantly increased HE risk. Yet, perhaps surprisingly, the reduction of the spot sign volume or its disappearance, called negative leakage rate, has been identified as the most significant dynamic risk feature of the spot sign.[81,82] This decrease or disappearance

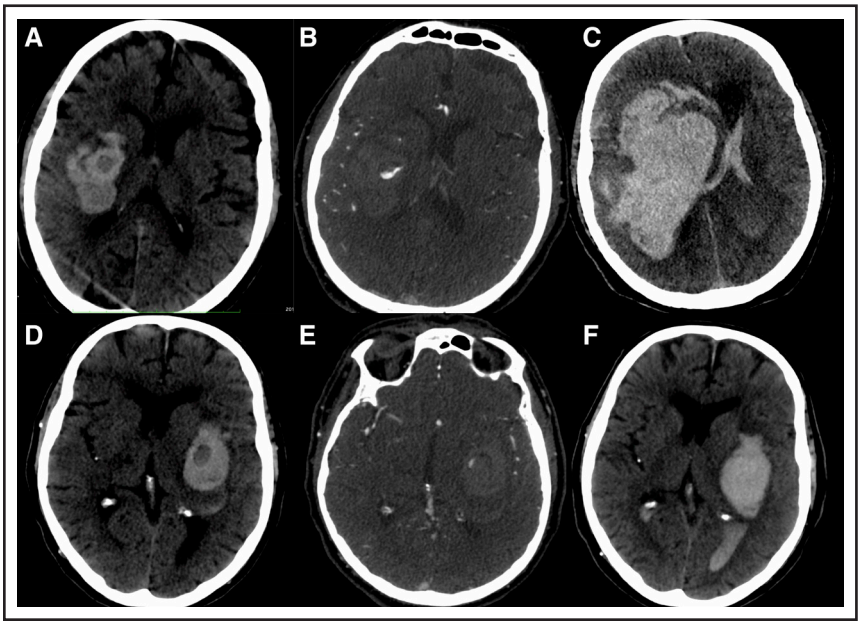

Figure 2. Illustrative cases of colocalization of hypodensity and spot sign.
Hypodensity signs on noncontrast computed tomography (CT; **A** and **D**) colocalized with spot signs on CT angiography (**B** and **E**). Follow-up noncontrast CTs showed a hematoma expansion of 197 mL (**C**) and 12 mL (**F**). Reproduced from Pensato et al[79] with permission. Copyright ©2024, European Stroke Organisation.

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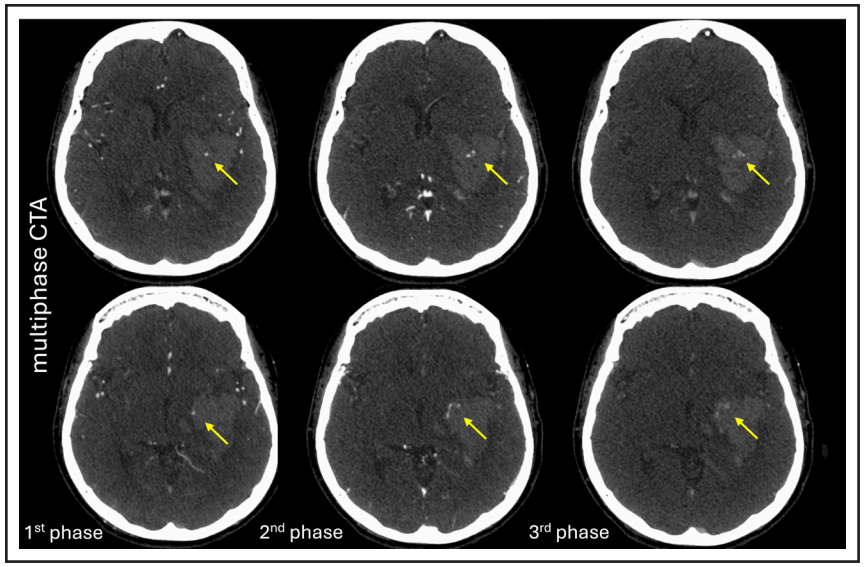

Figure 3. Illustrative case of spot sign volume modification over time. Multiphase computed tomography angiography (CTA) shows 2 spot signs first appearing in the first phase (yellow arrows), expanding in volume in the second phase acquired 10 seconds later (positive leakage rate), and then diminishing in volume due to contrast dilution into the hematoma in the third phase acquired 18 seconds later (negative leakage rate).

is likely linked to the expansion of contrast within the hematoma, resulting in a dilution effect that makes the spot sign appear to diminish in size as it diffuses into a larger area (pseudodecrease or parenchymal dispersion). Changes in CT density over time have been less extensively investigated, yet it arguably represents the other half of the spot sign evolution story.[73] A study demonstrated that an increase of at least 10% of Hounsfield unit in the spot sign region between CTA and delayed CT acquired 5 minutes later (called the leakage sign) increases both the sensitivity and specificity of the spot sign.[93]

MRI SPOT SIGN

Although contrast extravasation within the hematoma was first described on MRI,[23] most studies have focused on the CTA spot sign, reflecting the more widespread availability and use of CT in acute stroke care. The spot sign evaluated with contrast-enhanced T1-weighted MRI has been associated with a higher risk of HE and poorer functional outcomes.[95–97] Notably, the MRI spot sign has been described in up to 62% of patients with acute ICH, suggesting a higher sensitivity but lower specificity compared with the CTA spot sign.[95] This discrepancy may reflect differences in the timing between contrast administration and image acquisition, but also different spatial resolutions might play a role. More studies are needed to investigate both contrast and noncontrast MRI features associated with HE.

CONCLUSIONS AND FUTURE CLINICAL IMPLICATIONS OF THE SPOT SIGN

Current Gaps

The spot sign was initially enthusiastically embraced as a promising radiological marker for predicting HE with the potential to guide acute decision-making and imaging protocols for hemorrhagic stroke.[17,18,98] However, the lack of efficacy demonstrated in clinical studies investigating anti-HE treatments in patients selected based on spot sign status has raised doubts about the utility of this sign, and its assessment requires time, resources, and radiation exposure.[19–21,40,57] Therefore, a shift in patient selection for anti-HE trials has occurred, whereby early presentation time is now prioritized over imaging features.[53,54] Selecting patients within the early window allows targeting those with the smallest initial hematoma volume and the largest anticipated significant HE.[99] Nonetheless, more than half the patients who present in the early window have minimal or no HE risk.[99] Moreover, most patients present in the late window or, at least, beyond the early window.[3]

Current Clinical Implications of Advanced Imaging: Prognosis and Etiological Diagnosis

A significant barrier to spot sign implementation remains the limited use of CTA in acute ICH management. Acute CTA is a safe investigation that can also inform prognostication[14] and aid in the differential diagnosis of secondary ICH etiologies (eg, vascular malformations, cerebral venous thrombosis).[100,101] Therefore, CTA should be more widely implemented in acute ICH protocols, irrespective of the treatment interaction of anti-HE interventions with the spot sign.

Future Clinical Implications of Advanced Imaging: Treatment Decision-Making

Imaging-based selection remains a promising approach to guide also treatment decision-making. Notably, mounting evidence suggests that there are nuanced imaging findings in spot sign assessment that offer greater granularity and help stratify HE risk.[34,79–82,85,93] Scores that integrate these nuances represent promising tools that could

Table 4. Recommendations for Improvement and Future Implementation of the Spot Sign

Research needs	Example of future studies
1. Evaluation of high-risk features of the spot sign to predict HE	Investigators of a clinical study conduct a comprehensive assessment of the prediction performances (sensitivity, specificity, PPV, NPV, accuracy, and C statistic) for HE occurrence and severity of a new static or dynamic feature of the spot sign
2. Integration of spot sign high-risk features into HE prediction scoring system	Investigators use static or dynamic features of the spot sign (eg, Black-&-White sign), along with other imaging and nonimaging parameters, to develop and validate HE prediction scores.
3. Analysis of the treatment interaction effects of high-risk features of the spot sign targeting HE	Investigators of a randomized trial examining a new hemostatic treatment in ICH prespecify multiplicative 2-by-2 interaction terms (spot sign×study drug) in their protocol and statistical analysis plan.
4. Investigations of imaging features (including spot sign) associated with future hematoma growth rates	Investigators of a prospective clinical study assess HE in multiple time points (eg, follow-up CT acquired 1 and 24 h after baseline imaging) to evaluate noncontrast CT and CTA predictors of fast/early expansion (HE occurring within the first hour) and slow/late expansion (HE occurring between 1 and 24 h)
5. Assessment of the spot sign role in informing surgery strategies	Investigators explore earlier and more aggressive surgical treatment in spot sign–positive patients vs spot sign–negative patients with identical clinical presentations and approaches to a targeted surgical hemostasis.
6. Evaluation of the spot sign in Mobile Stroke Units.	Investigators of a Mobile Stroke Unit study evaluate the prehospital feasibility, interreader agreement, and predictive performances for HE of the CTA spot sign
7. Evaluation of MRI features associated with HE	Investigators of a clinical study involving patients with acute ICH with MRI as baseline imaging examine contrast (spot sign) and noncontrast MRI features associated with HE

CT indicates computed tomography; CTA, CT angiography; HE, hematoma expansion; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; NPV, negative predictive value; and PPV, positive predictive value.

potentially tailor anti-HE interventions. A personalized approach might also be pivotal from a cost-effectiveness standpoint, especially given the emergence of costly medical and surgical treatments now available for ICH.[102] Anticoagulation reversal agents, such as andexanet, with a per-patient cost exceeding 20 000 USD, are expected to be used more, given ANNEXA-I trial (Andexanet Alfa in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor) results.[10] The FASTEST trial ([Recombinant Factor VIIa for Acute Hemorrhagic Stroke Administered at Earliest Time]; with enrollment of patients <2 hours from symptom onset) may demonstrate rFVIIa benefit. Surgical options such as lobar ICH evacuation per the ENRICH protocol also have a high price tag and should ideally not target smaller ICH (≈20 mLs) if there are no features suggesting further HE.[61] Historically, the surgical management of ICH was usually delayed to allow for clot stability and easier clot removal, leading to actively excluding patients with positive spot signs. However, recent advances in minimally invasive surgery have enabled surgeons to identify active bleeding spots and apply surgical hemostasis in real-time, thus including surgery in the acute antihematoma strategies.[62,103] The presence of the spot sign and its nuances might play a major role, therefore, in informing both the selection of surgical candidates and optimizing the surgical approach to achieving durable hemostasis. In addition, the presence of a spot sign in an ICH located within the lenticulostriate territory, which is not amenable to surgical intervention, might guide endovascular approaches in the future aimed at achieving targeted endovascular hemostasis (ie, positioning the catheter in the M1 segment of the middle cerebral artery, with intermittent inflation and deflation to control bleeding).

The growing use of mobile stroke units using CT+CTA imaging protocols represents an opportunity to evaluate the treatment interaction effect of the spot sign in a prehospital setting and, potentially, facilitate the enrollment of more spot sign–positive patients in a future imaging-based clinical trial.[104] From the imaging standpoint, the advancement in CT technologies might significantly enhance the predictive performance of spot signs. For instance, photon-counting CT can detect the signal from individual X-ray photons rather than the total amount, allowing for better spatial resolution, improved image quality, and reduced artifacts.[105]

The ultimate goal is to integrate different clinical and radiological variables, including nuances of the spot sign, to develop novel HE scores that accurately determine both the risk and severity of HE—achieving high positive predictive value in the late window and high negative predictive value in the early window. Recommendations for future studies to enhance the clinical utility of the spot sign are summarized in Table 4. This could lead to more accurate prediction of HE and, more importantly, facilitate the bench-to-bedside translation of potential acute intracerebral hematoma intervention,[102] thereby expanding and refining our therapeutic armamentarium.

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