

Accuracy of spot sign in predicting hematoma expansion and clinical outcome

A meta-analysis

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Abstract

Background: Spot sign on computed tomography angiography (CTA) has been reported as a risk factor for hematoma expansion (HE) and poor outcome after intracerebral hemorrhage (ICH). We performed a meta-analysis to investigate the predictive accuracy of spot sign for HE, mortality risk, and poor outcome.

Methods: We searched PubMed, Embase, and the Cochrane Library for relevant studies. Studies were incorporated if they reported data on relationship between CTA spot sign and HE, mortality or poor outcome.

Results: Twenty-nine studies were pooled in this meta-analysis. The spot sign occurred in 23.4% patients with spontaneous ICH undergoing CTA scans. It showed a sensitivity of 62% (95% confidence interval [CI] 54–69), with a specificity of 88% (95% CI 85–91). Spot sign was related with increased risk of HE (odds ratios [OR] 8.49, 95% CI 7.28–9.90). In the analysis of association between spot sign and outcome, patients with spot sign had a significant higher risk of in-hospital death (OR 5.08, 95% CI 3.16–8.18) and 3-month death (OR 3.80, 95% CI 2.62–5.52). The spot sign was also a predictor of poor outcome at discharge (OR 6.40, 95% CI 3.41–12.03) and at 3 months (OR 4.44, 95% CI 2.33–8.46).

Conclusions: The overall incidence of CTA spot sign in spontaneous ICH patients is substantial. Spot sign demonstrated a good diagnostic performance in predicting HE and was closely associated with increased risk of death and poor outcome.

Abbreviations: AUC = area under the curve, CI = confidence interval, CT = computed tomography, CTA = CT angiography, DOR = diagnostic odds ratio, HE = hematoma expansion, ICH = intracerebral hemorrhage, mRS = modified Rankin Scale, NLR = negative likelihood ratio, OR = odds ratio, PLR = positive likelihood ratio, SROC = summary receiver operating characteristic.

Keywords: clinical outcome, hematoma expansion, intracerebral hemorrhage, meta-analysis, spot sign

1. Introduction

Spontaneous intracerebral hemorrhage (ICH) is the most devastating type of stroke, with a mortality up to 40% at 30 days after ictus and only one-fifth of the survivors could live independently after 6 months.^[1] Although most determinants of ICH outcome, such as hematoma location and baseline volume, are unmodifiable at presentation,^[2] clinically significant hemato-

ma expansion (HE), occurring in up to a third of patients with ICH,^[3] has been identified as one of the most important determinants of early neurological deterioration and poor clinical outcomes in spontaneous ICH patients.^[4,5] Many ICHs still expand at the time of initial emergency department assessment, causing increased risk of death or disability. Therefore, HE is a promising potential treatment target to improve prognosis of ICH.^[6,7] Hemostatic therapy may be efficient in preventing HE for patients with ICH, but it carries the risk of thromboembolic events in inappropriate patients. A reliable approach to accurately predict HE and further clinical outcome is of key importance for choosing potentially best therapeutic strategy for ICH.

Recently, spot sign, well acknowledged as unifocal or multifocal contrast enhancement within an acute spontaneous ICH visible on computed tomography angiography (CTA) source images and discontinuous from adjacent normal or abnormal blood vessels, has been regarded as a potential predictor of HE and risk factor of death or poor outcome.^[8] So far, the pathophysiological mechanisms of spot sign remained undefined with a series of possible explanations including breakdown of blood–brain barrier, microaneurysms, and pseudoaneurysms.^[9] Studies on spot sign differed in terms of population, imaging technique, onset-to-scan time, and definition of outcomes, resulting in a wide range of frequencies and predictive values across studies. Thus, we performed this meta-analysis to evaluate the predictive ability of spot sign for HE or poor outcome and try to define the factors that influence the accuracy.

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XX, JZ, and KY have contributed equally to this work.

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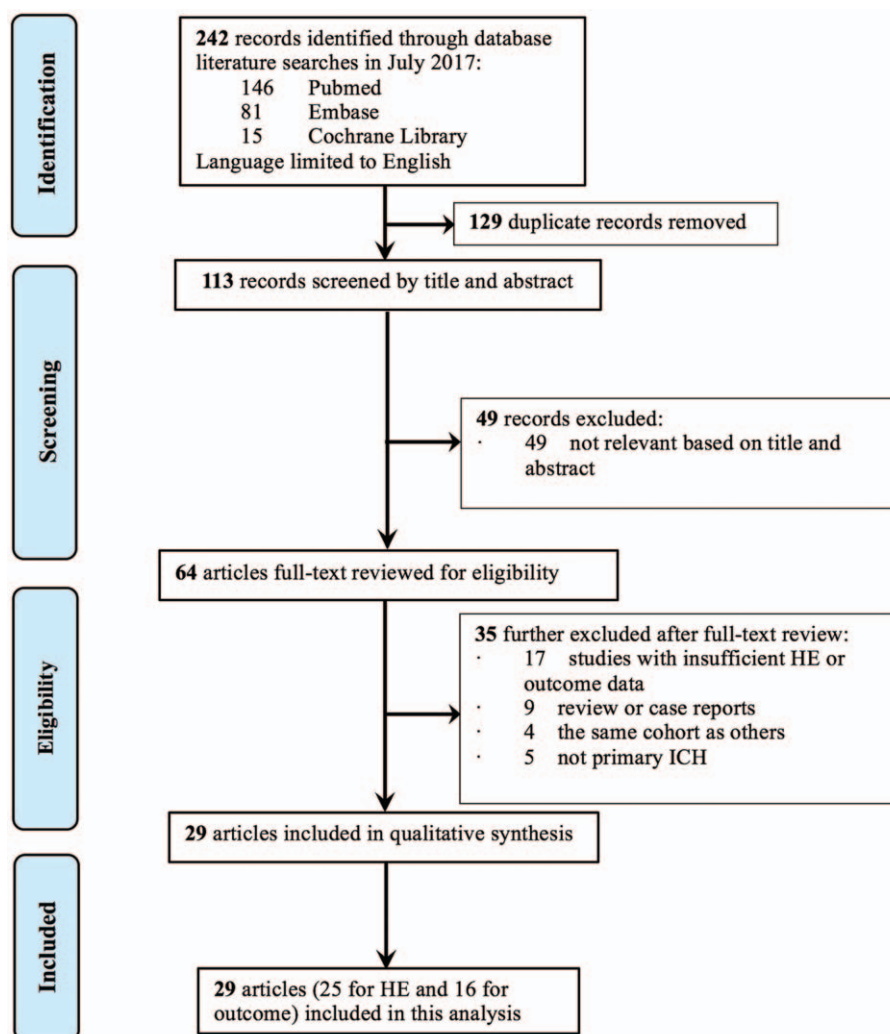


Figure 1. Flowchart of literature search and study selection for this meta-analysis.

2. Methods

2.1. Literature search and selection criteria

We performed this study following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. All analyses were based on previous published studies, thus no ethical approval and patient consent was required. We systematically searched PubMed, Embase, and the Cochrane Library between January 1995 and July 2017. ICH, spot sign (contrast extravasation), CTA, and their synonyms were the search terms. The language was restricted to English. Reference lists of the identified articles were also examined to identify studies that might be missed by database search. HE was defined as an increase in hematoma volume of >6 mL or >30% from the baseline volume.^[6,8] The primary outcome measurement of this analysis was HE and the secondary outcome measurements included death and poor clinical outcome measured by the modified Rankin Scale (mRS).

Two authors (XX and JZ) identified potentially relevant studies independently, resolving any disagreement or uncertainty by discussion. The final list of included studies was decided on consensus. Studies were included if they met the following inclusion criteria: original articles investigating CTA spot sign in

patients with spontaneous ICH (involving at least 20 cases); reported clear definition of HE which was in line with our standard; reporting or allowing calculation of prevalence, sensitivity, and specificity of spot sign in predicting HE, death, or poor outcome. Studies reporting patients with secondary ICH and case reports were excluded.

2.2. Data extraction and quality assessment

Two investigators (XX and JZ) independently reviewed the full text of selected studies and extracted necessary information using a standardized form. The following information was abstracted: author, design, study period, effective sample size, computed tomography (CT) modality, onset to CTA scan time, definition of HE, time from CTA scan to HE assessment, blindness, and outcome measurements (death or poor outcome defined as mRS \geq 3). Quality assessment for each study was by the QUADAS-2 tool and disagreements were resolved by discussion and consensus.

2.3. Statistical analysis

Data were pooled in a meta-analysis when at least three studies with relevant data were available. Results were combined using a

Table 1
Characteristics and methodological aspects of included studies.

Author	Study design	Country, period	Sample size	Male, %	Definition of HE	Time to CTA, h	CT modality	Time to HE assess, h	Blindness	Prognosis measurement
Wada	P	USA, 2004–2006	39	67	>6 mL or >30%	<3	CTA	<48	NA	In-hos mort
Goldstein	R	USA, 2002–2006	104	53	>33%	<48	CTA	<48	Yes	In-hos mort
Delgado	R	USA, 2000–2008	367	58	>6 mL or >30%	Mean: 7.4	CTA; first and delayed	<48	Yes	NA
Ederies	R	Canada, 2004–2008	61	67	>6 mL or >30%	<6	CTA; PCCT	<24	Yes	NA
Delgado*	R	USA, 2000–2008	573	54	>6 mL or >30%	Mean: 7.4	CTA	<48	Yes	In-hos mort, 3-mo PO
Park	P	Korea, 2007–2009	110	63	>6 mL or >30%	<24	CTA	<24	NA	3-mo mort
Rodriguez-Luna	P	Spain, 2009–2010	89	58	>6 mL or >33%	<6	CTA	<24	Yes	3-mo mort
Li	P	China, 2007–2010	139	68	>12.5 mL or >30%	<6	CTA	<24	Yes	In-hos mort/PO, 3-mo mort/PO
Wang	R	China, 2007–2010	312	57	>6 mL or >33%	<3	CTA	<24	NA	NA
Demchuk*	P	Multic, † 2006–2010	228	57	>6 mL or >33%	<6	CTA	<24	Yes	3-mo mort
Remero	P	USA, 2009–2010	131	61	>6 mL or >33%	<24	CTA	<24	NA	In-hos mort
Sun	P	China, 2009–2010	112	64	>6 mL or >30%	<6	CTA, CTP	<24	Yes	NA
Ciura	P	USA, 2012–2013	74	55	>6 mL or >33%	<24	CTA	<24	Yes	In-hos mort
Han	R	Korea, 2008–2012	187	50	>12.5 mL or >30%	<24	CTA	<24	NA	In-hos mort
Hotta	R	Japan, 2009–2012	198	58	>12.5 mL or >30%	<24	CTA	<24	NA	In-hos mort
Moon	R	Korea, 2005–2012	287	56	>6 mL or >33%	<12	CTA	<72	NA	1-mo mort
Ovesen	P	Denmark, 2011–2012	21	72	>12.5 mL	<4.5	CTA	<24	NA	Neurological deterioration
Rodriguez-Luna	P	Multic, † 2006–2012	320	NA	>6 mL or >33%	<6	CTA; first and delayed	<24	Yes	NA
Tsukabe	R	Japan, 2009–2014	83	63	>6 mL or >30%	<6	CTA; first and delayed	<24	Yes	NA
Brouwers	P	USA, 1994–2011	817	56	>6 mL or >33%	Med: 5	CTA; first and delayed	Med: 18	Yes	NA
Hou	R	China, 2012–2013	53	64	>33%	<6	CTA	<24	NA	NA
Kim	R	Korea, 2009–2011	316	NA	>6 mL or >33%	<24	CTA	<24	NA	NA
Boulouis	P	USA, 2012–2013	232*	53	>6 mL or >33%	Med: 3.2	CTA	<48	Yes	NA
Morotti	R	USA, 2001–2015	709	56	>6 mL or >30%	<48	CTA	<48	Yes	NA
Morotti*	R	USA, 2001–2015	49	55	>6 mL or >30%	<24	CTA	<48	Yes	In-hos mort, 1-mo mort
Rodriguez-Luna*	P	Multic, † 2006–2012	189	56	>6 mL or >33%	<6	CTA	<24	Yes	3-mo mort/PO
Wang	P	China, 2014–2015	72	75	≥6 mL or ≥33%	<6	CTP	<24	Yes	3-mo mort
Nishiyama	R	Japan, 2013–2016	177	60	≥12.5 mL or ≥33%	<6	CTA	<48	NA	In-hos mort
Romero	R	USA, 2009–2012	123	61	>6 mL or >33%	<24	CTA	<48	NA	In-hos mort

CT = computed tomography, CTA = CT angiography, CTP = CT perfusion, HE = hematoma expansion, hos = hospital, Med = median, mo = month, mort = mortality, Multic = multicenter, NA = not available, P = prospective, PCCT = postcontrast CT, PO = poor outcome (modified Rankin Scale ≥ 3), R = retrospective.

* Studies only included in the analyses of death and poor outcome.

† Multicenter including Canada, Germany, India, Poland, Spain, and USA.

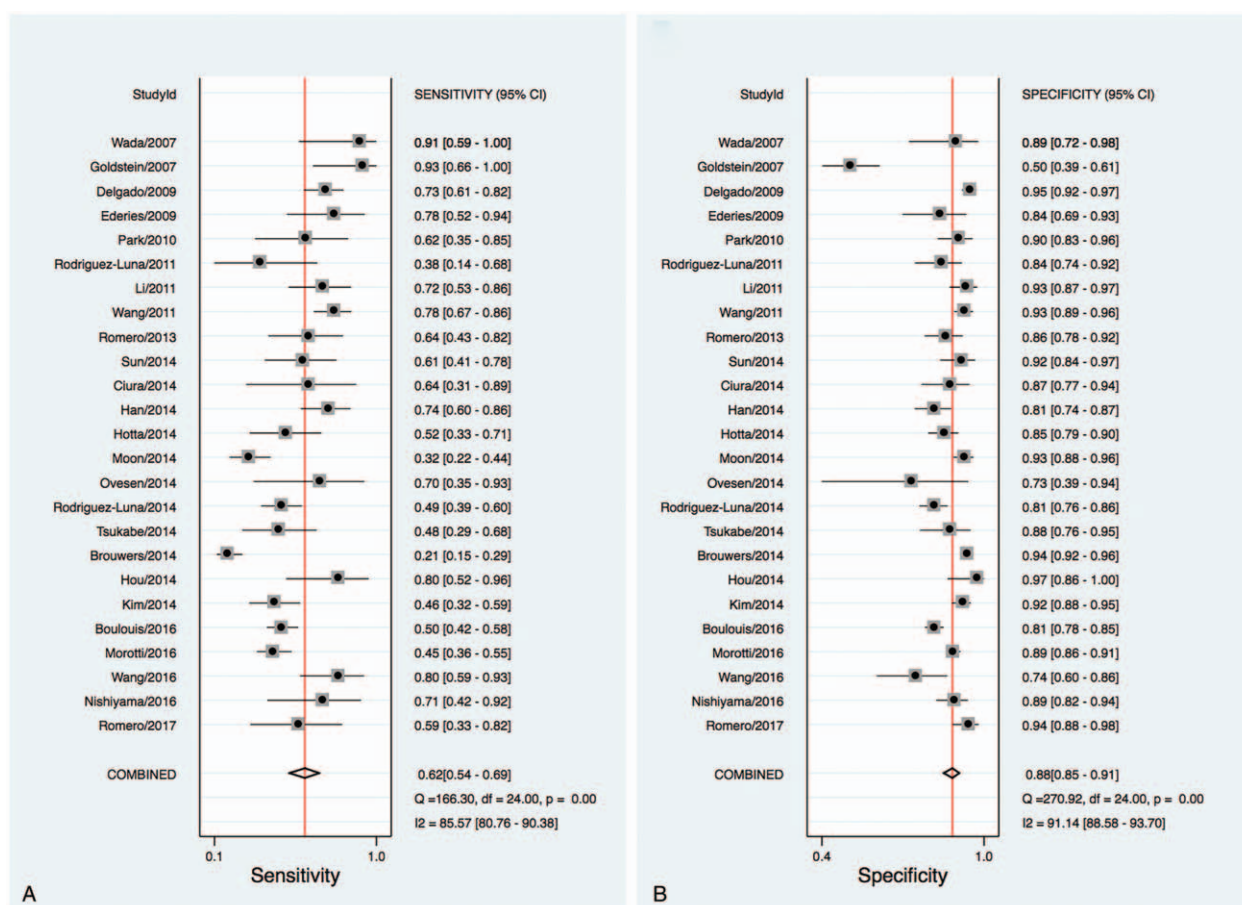


Figure 2. Forest plots of accuracy of CTA spot sign in predicting HE. Meta-analysis of the sensitivity (A) and specificity (B) of spot sign in predicting HE. CTA = CT angiography, HE = hematoma expansion.

random-effects model with DerSimonian–Laird approach. The positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR), as well as sensitivity and specificity were calculated. The strength of association between spot sign and HE, death, or poor outcome (mRS ≥ 3) were quantified by the odds ratio (OR) and their corresponding 95% confidence interval (CI), using the inverse-variance weighting method for aggregation. Heterogeneity between studies was assessed by Q test and I^2 statistics. For qualitative interpretation of heterogeneity, I^2 values of at least 50% were considered to represent moderate degree of heterogeneity, while I^2 values of at least 75% indicated high heterogeneity. Summary receiver operating characteristic (SROC) curves were constructed and area under the curve (AUC) was calculated. Publication bias was evaluated both graphically using a funnel plot and with the Egger statistical test. Subgroup analyses were conducted to explore the possible origin of heterogeneity. A P value of $<.1$ indicated heterogeneity or publication bias. Meta-analyses were conducted using the Stata/MP 14.1 (Stata Corp, TX).

3. Results

3.1. Characteristics of included studies

Systematic search of PubMed, the Cochrane Library, and Embase yielded 146, 81, and 15 results, respectively. After removing duplicates, we identified 64 relevant original studies by screening the titles and abstracts. Thirty-one studies were further excluded,

including 14 studies with no detailed records of HE or outcome, 5 studies of nonspontaneous ICH, four review articles, 5 case reports, and three studies used HE definitions contradictory to our criteria. Four studies conforming with the inclusion criteria were also excluded since they reported the same cohorts as other studies and only studies with the largest sample size and detailed information were included in our analysis.^[10–13] Finally, 29 studies were included in this meta-analysis (Fig. 1). Characteristics of included studies, methodological key issues, and quality indicators were summarized in Table 1. Among all the studies, four were only included in the analysis of death or poor outcome since these data on HE had been incorporated in other studies.^[14–17] Finally, 25 studies containing 5514 patients were pooled in to analyze the sensitivity and specificity of CTA spot sign in predicting HE,^[4,7–9,18–38] 10 studies were pooled in to analyze risk of in-hospital death in ICH patients with CTA spot sign,^[4,8,9,21,23,25–27,37,38] six studies for analysis of risk of 3-month death,^[15,16,19–21,36] three studies for risk of poor outcome at discharge,^[21,25,26] and four studies for analysis of risk of 3-month poor outcome.^[14,16,21,23] From inspection of each included study, spot sign positive group and spot sign negative group were the same in basic characteristics (age, gender, or stroke severity).

3.2. Spot sign and prediction for HE

The crude prevalence of spot sign on CTA was 23.4% (95% CI 19.9–26.9) in patients with spontaneous ICH. The random-effects

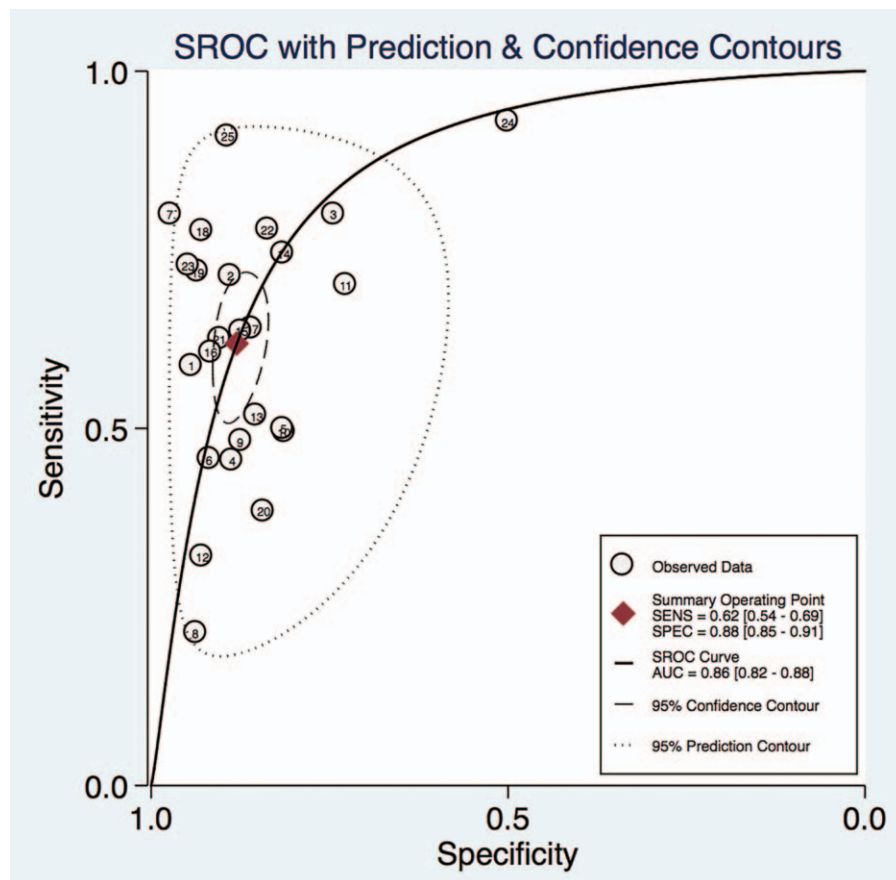


Figure 3. Summary receiver operating characteristic curve of spot sign for predicting hematoma expansion. The regression line summarizes the overall predictive accuracy. AUC = area under the curve.

pooled incidence of HE was 21.2% (95% CI 18.6–23.7): 57.5% (95% CI 50.9–64.0) among patients with spot sign versus 10.6% (95% CI 8.4–12.8) in patients without. There was significant correlation of spot sign with increased risk of HE (pooled OR 8.49, 95% CI 7.28–9.90; $P < .001$, $I^2 = 75.8\%$). Spot sign yielded a combined sensitivity of 62% (95% CI 54–69) and a specificity of 88% (95% CI 85–91) for predicting HE (Fig. 2). The combined PLR was 5.2 (95% CI 4.1–6.5), the summary NLR was 0.43 (95% CI 0.35–0.53), and the DOR was 12 (95% CI 8–17).

The SROC curve produced an AUC of 0.86 (Fig. 3), which meant that spot sign had a fine prediction ability for HE. The Q test demonstrated significant heterogeneity ($P < .01$) and visual inspection of the funnel plot and the Deeks test ($P = .03$) revealed publication bias. We further performed subgroup analyses in the

light of study design, blind assessment, sample size, and publication year (Table 2). Studies with a sample size no more than 130 and studies published in 2012 or earlier tended to produce higher sensitivity while specificity was easily influenced by all the stratifications (Fig. 4).

3.3. Spot sign and clinical outcomes

In the analysis of in-hospital mortality, 10 studies containing 1900 patients were included. The pooled in-hospital mortality rate was 41.3% (95% CI 29.5–53.1) in patients with spot sign versus 12.8% (95% CI 7.9–17.7) in patients free of spot sign ($P < .01$). Risk of in-hospital death was much higher in patients with evidence of spot sign, when compared with patients without

Table 2
Subgroup analyses concerning the sensitivity and specificity of CTA spot sign for predicting hematoma expansion.

Parameter	Category	Studies	Sensitivity	P1	Specificity	P2
Pro design	Yes	12	0.59 [0.47–0.71]	0.21	0.87 [0.82–0.92]	0.00
	No	13	0.64 [0.53–0.75]	—	0.88 [0.84–0.92]	—
Blindness	Yes	13	0.59 [0.48–0.70]	0.16	0.86 [0.82–0.90]	0.00
	No	12	0.65 [0.53–0.76]	—	0.89 [0.85–0.93]	—
Sample size	> 130	13	0.56 [0.45–0.66]	0.03	0.89 [0.86–0.92]	0.00
	≤ 130	12	0.69 [0.58–0.80]	—	0.86 [0.81–0.91]	—
Pub year	> 2012	18	0.56 [0.47–0.65]	0.01	0.88 [0.85–0.91]	0.00
	≤ 2012	7	0.75 [0.63–0.87]	—	0.87 [0.81–0.93]	—

CTA=computed tomography angiography, Pro design=prospective design, Pub year=study publication year.

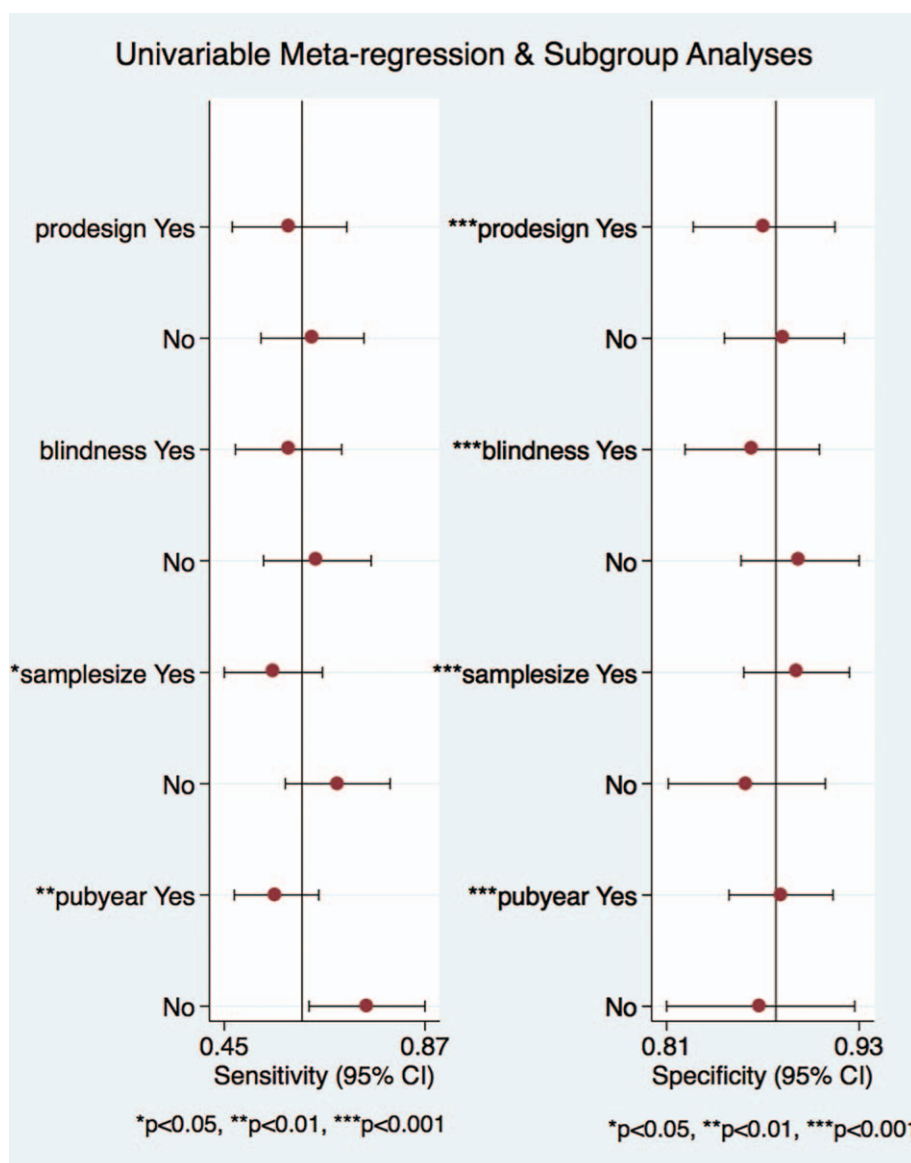


Figure 4. Univariable meta-regression and subgroup analyses of sensitivity and specificity of spot sign for hematoma expansion.

(pooled OR 5.08, 95% CI 3.16–8.18; $I^2 = 65.0\%$) (Fig. 5A). For the evaluation of 3-month mortality, we were able to include six studies containing 810 patients. Similarly, the risk of 3-month death in patients with spot sign was 3.8 times that of patients without spot sign (pooled OR 3.80, 95% CI 2.62–5.52; $I^2 = 0.0\%$) (Fig. 5B). No obvious publication bias in the analysis of mortality was uncovered by examination of the funnel plot.

Three studies including 444 patients and 4 studies containing 857 patients were pooled in the analyses of in-hospital and 3-month poor outcome, respectively. At discharge, 89.9% (95% CI 84.3–95.6) patients with spot sign got a poor outcome (mRS ≥ 3) while 59.3% (95% CI 35.9–82.7) patients without spot sign got a poor outcome ($P < .01$). Spot sign was a risk factor of poor outcome at discharge (pooled OR 6.40, 95% CI 3.41–12.03; $I^2 = 0.0\%$) (Fig. 5C). At 3-month follow-up, the percentage of poor outcome was 68.2% (95% CI 45.0–91.5) in patients with spot sign versus 34.3% (95% CI 21.8–46.9) in patients without ($P < .01$). The risk of poor outcome at 3-month follow-up was

much higher in patients with spot sign (pooled OR 4.44, 95% CI 2.33–8.46; $I^2 = 56.5\%$) (Fig. 5D).

4. Discussion

It has been well acknowledged that the initial hemorrhage volume is not static but frequent progresses due to continued bleeding and rebleeding, generally within the early hours after ictus.^[39] HE is shown to occur in up to 38% patients, most commonly in the first 6 hours after symptom onset.^[40] HE is an independent predictor of mortality and diminished functional outcome, while CTA spot sign is a recently validated predictor of HE in patients with spontaneous ICH.^[8] The relationship between spot sign and HE has been ever reviewed,^[41,42] however, only limited studies were included in that study. The association between number of spot sign and mortality or poor outcome had never been quantitative assessed. More comprehensive and updated studies reporting both HE data and clinical outcome data were incorporated in our study.

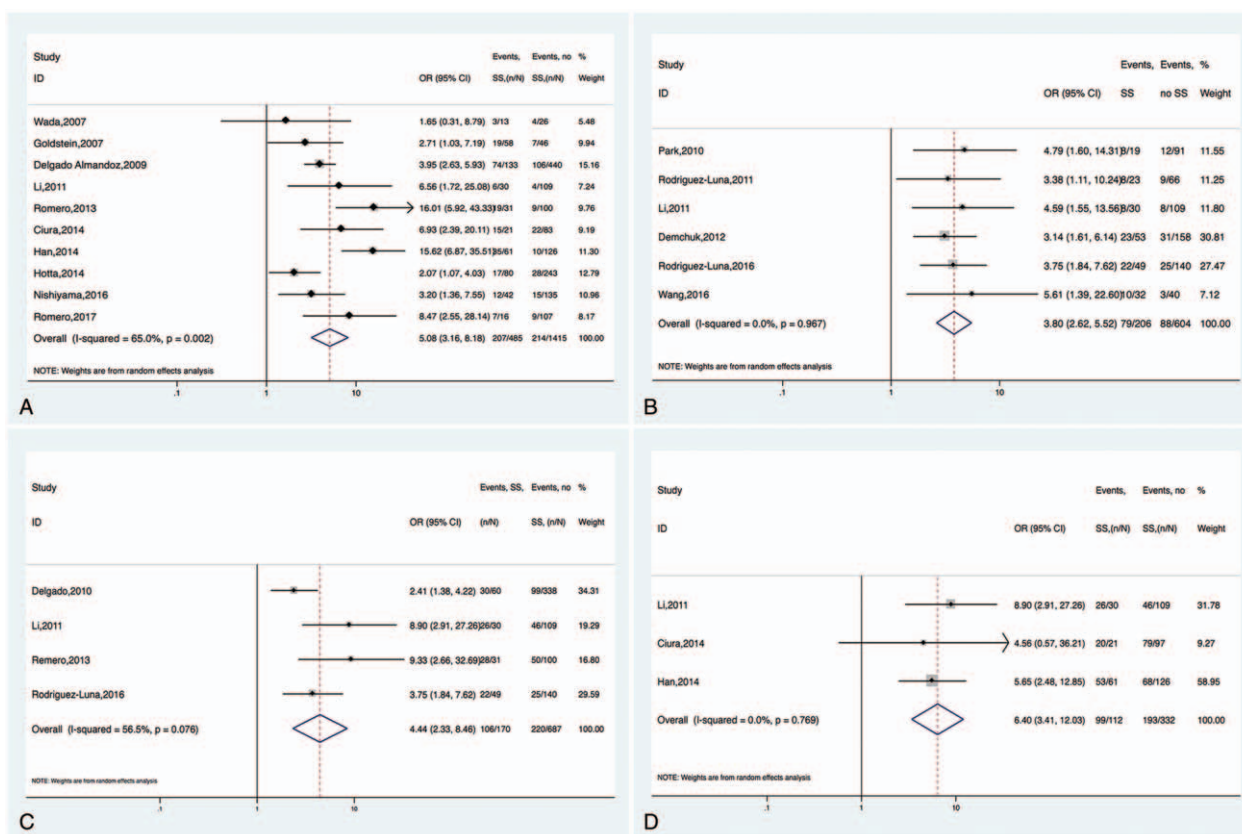


Figure 5. Forest plots of spot sign and risk of death or poor outcome. (A) In-hospital death; (B) 3-month death; (C) 3-month poor outcome; and (D) poor outcome at discharge. Poor outcome was defined as mRS ≥ 3 . mRS = modified Rankin Scale, OR = odds ratio, SS = spot sign.

Since most studies included did not perform a delayed phase CTA, data in the meta-analysis were spot sign on first-pass CTA when applicable. Our results demonstrated that CTA spot sign had a moderate sensitivity (62%) and a high specificity (88%) for predicting HE. Interestingly, four studies investigating both first-pass and delayed CTA showed that the frequency of spot sign in the delayed CTA acquisitions was higher than in the first-pass CTA.^[4,25,30,31] Further analysis of delayed CTA spot sign showed a much higher sensitivity (79%) and a slightly lower specificity (84%) for predicting HE. Study by Sun et al showed that the combination of CT perfusion could also improve the accuracy of spot sign in prediction of HE.^[24] Ederies et al reported that combination of postcontrast CT leakage with CTA spot sign increased the sensitivity from 78% to 94%.^[18] Nevertheless, the results were based on only four studies and more investigations are needed to verify this finding. The explanation for above changes might be that spot sign is a dynamic process and delayed imaging may help explore it with increased time interval during which the contrast can circulate

and infiltrate into the region of hematoma. Combination of CTA with other different CT modalities add to the accuracy for predicting HE; however, adding a CT modality is expected to increase the radiation dose and the risk-benefit ratio should be carefully judged and weighed before widespread application.

Spot sign is a strong predictor of poor outcome (mRS ≥ 3) and increased mortality risk both at discharge and at 3-month follow-up. According to previous research findings, major predictors of increased early mortality and adverse outcome during the acute phase of ICH are HE, intraventricular hemorrhage with obstructive hydrocephalus, and hyperglycemia.^[4,3] Spot sign is usually associated with larger hemorrhage volume, a more severe clinical presentation, and has a quite high accuracy in predicting HE. These reasons may partially explain the association between spot sign and clinical outcomes. The sensitivity and specificity of spot sign for predicting clinical outcomes was summarized in Table 3. Since only 3 studies reported the rate of poor outcome at discharge, this sensitivity and specificity was incomputable. On the whole, the accuracy of spot sign for predicting clinical

Table 3
Accuracy of spot sign for predicting clinical outcomes.

Clinical outcomes	Study, n	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC (95% CI)
In-hos mortality	10	53% (43–64)	81% (74–87)	2.9 (2.1–4.0)	0.57 (0.46–0.71)	5 (3–8)	0.74 (0.70–0.77)
3-mo mortality	6	49% (38–59)	80% (74–85)	2.4 (1.9–3.1)	0.64 (0.53–0.77)	4 (3–5)	0.71 (0.67–0.75)
3-mo poor outcome	4	34% (26–43)	89% (82–93)	3.1 (1.9–5.0)	0.74 (0.65–0.84)	4 (2–7)	0.69 (0.65–0.73)

3-mo = 3-month, AUC = area under curve, CI = confidence interval, dis = discharge, DOR = diagnostic odds ratio, in-hos = in-hospital, NLR = negative likelihood ratio, PLR = positive likelihood ratio.

outcomes was much lower than that for predicting HE. The definition of clinical outcome varied across studies and the variety in clinical outcomes was susceptible to outcome reporting bias.

While the mechanisms of HE are still not well understood, both primary and secondary vessel injury hypotheses have been proposed. It is important to note that the presence of the dynamic spot sign within hematoma may reflect ongoing bleeding, and most of the spot signs occurred in the arterial phase, suggesting small artery damage and bleeding. The success of emergent and future interventions aimed at preventing HE and subsequent poor outcome, including hemostatic drugs, will likely depend on the accurate selection of patients at risk of HE and poor outcome.^[25,26]

There are several limitations that should be acknowledged in this study. First of all, time from onset to CTA examination and patient's baseline ICH volume varied across studies. Caution should be taken that there was obvious publication bias and heterogeneity between studies for HE prediction. Besides, the number of studies reporting spot sign and clinical outcome was limited with small sample size. A large proportion of studies were retrospective and unblinded, adding to the risk of selection bias. Finally, the timing of scan, scanner type, scanning parameters, and injection method of contrast might also be confounding factors which were generally unclear and variable across studies.

5. Conclusions

In conclusion, the overall incidence of CTA spot sign after spontaneous ICH was substantial. Our study demonstrated that the CTA spot sign appeared to be a strong risk factor of death and poor clinical outcome as well as a potential imaging biomarker of HE in patients with spontaneous ICH. Further standardized studies are needed to better investigate the mechanism of HE and the association between spot sign and clinical outcome.

Author contributions

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Visualization: Jiashu Zhang.

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Writing – review and editing: Xinghua Xu, Jiashu Zhang, Kai Yang, Qun Wang, Bainan Xu, Xiaolei Chen.

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