Review

Cerebrovascular Diseases

Cerebrovasc Dis 2014;37:268–276
DOI: 10.1159/000360754

Received: October 28, 2013
Accepted: February 18, 2014
Published online: April 24, 2014

Accuracy of the Spot Sign on Computed Tomography Angiography as a Predictor of Haematoma Enlargement after Acute Spontaneous Intracerebral Haemorrhage: A Systematic Review

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Key Words
CT angiography · Haematoma enlargement · Intracerebral haemorrhage · Prognosis · Spontaneous intracerebral haemorrhage · Spot sign

Abstract
Background: A common early complication of intracerebral haemorrhage (ICH) is haematoma enlargement (HE), a strong independent predictor of a poor outcome. Therapeutic options to limit haematoma progression are currently scarce. Haemostatic therapy may be effective in patients with ICH, but it carries the risk of thromboembolic events in unselected patients. Accurate patient selection would, therefore, be of key importance for delivering potentially successful therapeutic strategies. Currently, there is no gold standard to accurately predict HE. The presence of contrast extravasation within the haematoma on computed tomography angiography (CTA), the 'spot sign', has been reported in several studies and seems a particularly promising marker but lacks a standardised evaluation so far. ***Summary:*** We conducted a systematic review of published data to address the research question: In adults with acute spontaneous ICH, how accurately does the spot sign predict HE on follow-up imaging and thus poor functional outcome or mortality? We searched PubMed and Embase databases (from 1980 to May 2012), using a highly sensitive search strategy and including all studies involving adult patients with spontaneous ICH evaluated with CTA and follow-up CT scans, reporting any measure of clinical outcome, and reporting or allowing calculation of accuracy measures of the spot sign in predicting HE and clinical outcome. Baseline characteristics, accuracy measures and effect measures, as well as bias assessment, were reported according to PRISMA recommendations. The quality of the studies was appraised using an adapted version of the REMARK reporting recommendations. From 259 potentially relevant studies, we finally selected 6 studies (1 of them was a multicentre cohort study) covering a total of 709 patients. Studies varied substantially in terms of size, methodological quality, definitions of terms, outcomes selected and results. In particular, definition of the spot sign was not consistent in all studies. Furthermore, the only outcome measure consistently available was HE, while definitions and analyses of clinical outcomes seemed not adequate. Lastly, the choice of candidate variables for univariate and multivariate analyses did not include all determinants of HE and poor functional outcome. High heterogeneity was demonstrated (I^2: 94% for HE) with substantial potential of

1015–9770/14/0374–0268$39.50/0

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bias. ***Key Messages:*** Studies of the spot sign are diverse and therefore complex to interpret. Our research question could not be answered due to heterogeneity and potential of bias in the selected studies. Further appropriately powered studies using standardised definitions and taking all predictors of HE and poor clinical outcome into account are required for a proper clinical implementation.

Introduction

Intracerebral haemorrhage (ICH) accounts for approximately 10–30% of all strokes among high- and low/middle-income countries, respectively [1], and has an overall ICH case fatality at 1 month of about 40% (range 13–61%) in almost all regions [2].

A common early complication of ICH is haematoma enlargement (HE), which affects about 30% of patients presenting within 3 h of onset and up to 70% within 24 h of onset, and is a strong independent predictor of a poor outcome [3–5]. Therefore, early HE identification could help to stratify patients on the basis of their risk profile and thus guide clinicians' decisions on treatment [6]. Therapeutic options to limit haematoma progression are currently scarce. Besides blood pressure control, haemostatic therapy, particularly with recombinant factor VIIa, may be effective in accurately selected ICH patients [5].

A promising marker of HE is the presence of contrast extravasation within the haematoma on computed tomography angiography (CTA). Firstly described in 1999 [7, 8], the presence of enhancing foci of contrast extravasation or the 'spot sign' in the setting of actively bleeding ICH has been demonstrated in about a third of the patients in several single-centre studies [9, 10].

Recently, a multicentre prospective observational cohort study confirmed previous findings [11], but the sensitivity of the spot sign in predicting HE was relatively low and not all predictors of HE or poor functional outcome were included in the analysis [12].

Nevertheless, the spot sign is being used in ongoing clinical trials (e.g. the Spot Sign for Predicting and Treating ICH Growth Study, STOP-IT Study – ClinicalTrials.gov NCT00810888, the 'Spot Sign' Selection of Intracerebral Haemorrhage to Guide Haemostatic Therapy, SPOTLIGHT Study – ClinicalTrials.gov NCT01359202, and the Spot Sign and Tranexamic Acid on Preventing ICH Growth – Australasia Trial, STOP-AUST – ClinicalTrials.gov NCT01702636) as a tool to stratify patients for treatment.

To date, results from individual studies have not been systematically summarised. Therefore, our study aimed to answer the research question: In the adult population with acute spontaneous ICH, how accurately does the presence of contrast extravasation on CTA, the spot sign, predict HE on follow-up imaging and subsequent poor outcome [defined as death or long-term disability – the latter measured by the National Institutes of Health Stroke Scale (NIHSS) [13] and/or modified Rankin Scale (mRS)] [14]?

Methods

A systematic review of the literature was conducted using secondary data analysis of published studies, and, therefore, ethical approval and data protection permissions were not required.

All available studies (including case series, cohort, case-control and randomised trials) were included if the following inclusion criteria were met: patients ≥18 years of age with confirmed spontaneous ICH evaluated with CTA and follow-up CT scans, studies reporting any measure of clinical outcome (NIHSS, mRS or death), and reporting or allowing calculation of sensitivity and specificity (with confidence intervals, CI), positive and negative predictive values, positive and negative likelihood ratios, prevalence and accuracy of the 'spot sign' in predicting haematoma growth and clinical outcome. Studies including patients with secondary ICH and case reports were excluded.

A highly sensitive search strategy with different combinations of appropriate key words was developed (see online suppl. appendix 1; for all online suppl. material, see www.karger.com/doi/10.1159/000360754). Two reviewers (A.D.G. and D.D.A.) independently searched PubMed and Embase from 1980 (when CT became widely available) to the end of May 2012 (as late as project resources permitted). Reference lists, related articles and citation lists of each of the papers identified in the initial searches were screened in order to identify any further relevant papers. Grey literature (conference abstracts, letters and editorials) was reviewed separately; however, due to resource constraints, full quality assessment was not conducted on this material. Where a duplicate publication was identified, the main report or the most informative cohort was included in the review.

Initial screening of study titles excluded non-relevant topics and remaining studies were further screened by reading abstracts. The final eligible studies and any supplementary material were read in full.

A quality assessment tool and a data extraction form were produced and piloted. Data were independently extracted using this form (see online suppl. appendix 2), with disagreements during this process resolved with a third referee (I.W.). No assumptions were made to derive data. No additional data were obtained from the investigators.

There are currently no guidelines for quality assessment of prognostic studies [15]. Therefore, a novel quality assessment tool, which was based on items in the REMARK recommendations for prognostic tumour markers [16], was developed.

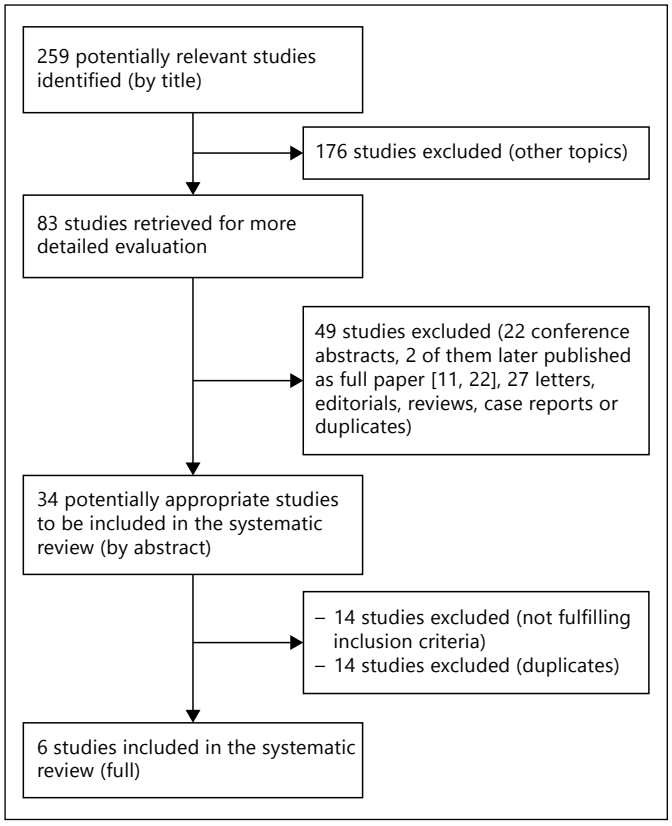

Fig. 1. Literature search.

Where results were not reported directly or were incomplete (for instance without CI), these were calculated, where possible, based on data provided in the paper. Data were managed using Excel software and analysed using Stata 10.0 statistical software.

For the radiological outcome, the only outcome consistently available, a funnel plot was drawn to estimate the risk of publication bias. Formal tests for funnel plot asymmetry were not carried out given the few studies included [17]. An exploratory test for heterogeneity (I^2 statistics) was performed [18].

Table 1. Studies not fulfilling the inclusion criteria of the present systematic review

Authors	Reason(s) for exclusion
Becker et al. [7]	No follow-up CT
Brouwers et al. [2, online]	Follow-up CT available only for subgroup analysis (228 patients) Accuracy measure for radiological and clinical outcome not available/calculable
Delgado et al. [3, online]	Age criterion not fulfilled (range 6–94 years) No data on clinical outcome
Delgado et al. [24]	Age criterion not fulfilled (range 8–94 years)
d'Esterre et al. [42]	Definition of ICH not specified Accuracy measures not available/calculable
Ederies et al. [6, online]	Definition of ICH not specified Accuracy measures for clinical outcome not available/calculable
Evans et al. [7, online]	Accuracy measures for clinical outcome not available/calculable
Gazzola et al. [20]	Accuracy measures for radiological and clinical outcome not available/calculable
Hallevi et al. [19]	Age not specified Accuracy measures for clinical outcome not available/calculable
Kim et al. [10, online]	Accuracy measures for radiological outcome not available/calculable
Murai et al. [8]	Definition of ICH not specified Data on clinical outcome not available
Romero et al. [12, online]	Accuracy measures for radiological and clinical outcome not available/calculable
Thompson et al. [13, online]	Accuracy measures for radiological and clinical outcome not available/calculable
Wang et al. [14, online]	Definition of ICH not specified Accuracy measures for clinical outcome not available/calculable

Results

Figure 1 depicts the study selection. Of 34 potentially eligible studies, 14 did not fulfil our inclusion criteria (table 1; references partly in online suppl. appendix 3). The remaining 14 studies which were excluded were duplicates. Six studies were included in this review [9–11, 21–23].

Table 2 provides the main characteristics of the selected studies. The median recruitment period was 2 years (interquartile range 1–4; for the years from 2004 to 2010) and the total number of patients included was 709 (median = 107).

Data on Glasgow Coma Scale and NIHSS score were available for all studies, except for the study by Wada et al. [9]. Among the baseline characteristics reported to be associated with HE and poor outcome, use of oral anticoagulants or anti-platelet agents, blood pressure values and glucose values on admission were always considered. Furthermore, Demchuk et al. [11], Goldstein et al. [10] and Li et al. [22] also collected data on previous stroke.

Quality was assessed according to themes in the adapted REMARK form. All the selected papers but 1 [10] re-

Table 2. Main characteristics of the studies selected

Authors	Publication, year	Country	Population, n	Median or mean age (range/±SD)
Demchuk et al. [11]	2012	Canada, Spain, Germany, Poland, India, USA	228	Spot +: 73 (38–90) Spot –: 70 (21–100)
Goldstein et al. [10]	2007	USA	104	Spot +: 74 (69–81) Spot –: 72 (63–78)
Li et al. [22]	2011	China	139	Overall: 55 (19–80)
Park et al. [21]	2010	South Korea	110	Overall: 62 (33–88) Spot +: 61 (±16) Spot –: 60 (±14.1)
Rodriguez-Luna et al. [23]	2012	Spain	89 with CTA/ 133 total	Overall (for all 133 patients): 71.7 (±11.8)
Wada et al. [9]	2007	Canada	39	Overall 64 (31–85)

ported prospective cohort studies enrolling mainly consecutive patients (they did not specify the sampling strategy). In the study by Goldstein et al. [10], data were collected retrospectively and reviewed from an ongoing prospective cohort study on outcome after ICH. Only the study by Demchuk et al. [11] involved multiple centres. All studies reported defined inclusion and exclusion criteria and the enrolment period. Patients were followed up for 3 months in all studies except 1 study [10], which only reported in-hospital mortality. A sample size calculation was provided in 2 studies [10, 11] on the basis of the primary outcome (haematoma growth). Candidate variables, characteristics potentially associated with the outcome variable and to be included in univariate analyses, were always listed. Spot sign/contrast extravasation and pre-specified radiological and clinical outcomes were fully defined in all but 1 paper [23] and varied considerably across studies (table 3). Furthermore, Demchuk et al. [11] reported that the definition of the spot sign was not established at the beginning of the study, although not affecting their inter-rater agreement (k = 0.72).

Assessment of prognostic markers and outcomes was mainly blinded. Park et al. [21] and Wada et al. [9] did not report blinding. Demchuk et al. [11] and Wada et al. [9] provided the most detailed descriptions of statistical analyses, both reporting accuracy measures for the predictive ability of the spot sign as a pre-specified outcome. One paper reported limited statistical analysis (not including multivariate analysis) [21]. Variables were pre-specified for the multivariate analysis in only 2 papers [9, 11]. All studies but 1 [21] accounted for the number of patients excluded or dropouts. Only Demchuk et al. [11] reported how missing data were handled.

Regarding prognostic marker assessment, CTA images were obtained in 1 study within 3 h [9], 3 studies within 6 h [11, 22, 23] and in the other 2 studies by 24 h. Only in the study by Wada et al. [9] second-pass images were obtained.

The assessment of HE occurred 1–2 days after haemorrhage onset. The location of the haematoma was reported by all authors but Demchuk et al. [11]. In 2 papers [10, 11], radiological outcome was specifically considered the primary outcome.

Table 4 shows reported and/or calculated accuracy measures for the ability of the spot sign in predicting HE. Table 5 shows the effect measures for the ability of the spot sign to predict HE obtained from the 2 × 2 contingency tables at univariate analysis.

Results of the multivariate analysis for the same effect measures were reported by Demchuk et al. [11] (relative risk 2.6, 95% CI 1.8–3.7, including the following parameters in the model: baseline ICH volume, time from onset to CTA, age >80 years, male sex, hypertension, diabetes mellitus, anti-platelet use, anti-coagulation use, systolic blood pressure >200 mm Hg, and NIHSS ≥18) and Goldstein et al. [10] (odds ratio 18, 95% CI 2.1–162, including age, time to CTA, admission systolic blood pressure and haematoma volume in the model). Table 6 reports accuracy measures for the ability of the spot sign to predict clinical outcomes.

Data from the cohort studied by Wada et al. [9] were obtained from a stacked bar graph reporting percentages

Table 3. Definition of the spot sign, HE and clinical outcome across studies

Authors	Spot sign/contrast extravasation definition	HE definition	Clinical outcome definition
Demchuk et al. [11]	Four criteria: (1) serpiginous or spot-like appearance within the margin of a parenchymal haematoma without connection to an outside vessel; (2) contrast density >1.5 mm in diameter in at least one dimension; (3) contrast density (Hounsfield units) at least double that of the background haematoma, and (4) no hyperdensity at the corresponding location on non-contrast CT	Substantial HE at follow-up CT defined as an absolute growth >6 ml or relative growth >33% from initial CT Other definitions of HE were also explored as a secondary analysis because no consensus existed on the preferred cut-off for clinically significant HE	(1) Early neurological worsening (≥4 points in the NIHSS score at 24 h vs. baseline) (2) mRS score at 3 months (median) (3) Mortality at 3 months
Goldstein et al. [10]	The presence of contrast extravasation was operationally defined as the presence of high-density material within the hematoma	An increase in volume of >33% from baseline	In-hospital mortality
Li et al. [22]	On multidetector CTA radiological criteria: (1) ≥1 focus of contrast pooling within the ICH; (2) with an attenuation ≥120 Hounsfield units; (3) discontinuous from the normal or abnormal vasculature adjacent to the ICH, and (4) of any size and morphology [3, online]	An increase in hematoma volume >33% or >12.5 ml was considered as HE	(1) In-hospital mortality (2) Poor outcome at discharge (mRS >2; analysed as dichotomised variable, mRS 0–2 vs. 3–6) (3) Mortality at 3 months (4) Poor outcome at 3 months (mRS >2; analysed as above)
Park et al. [21]	One or more 1- to 2-mm-sized foci of enhancement within the haematoma on axial view of 3D-CTA source images; an ovoid or round shape of foci was also included as the spot sign; the location of the spot sign was inspected as a centre or peripheries of haematoma	An increase in volume >30% or >6 ml from the baseline brain CT scan by the criteria of Wada et al. [9]	(1) Mortality at 3 months [(2) Clinical deterioration; accuracy measures neither reported nor calculable]
Rodriguez-Luna et al. [23]	Definition not provided in the Methods	Ultra-early haematoma growth (defined as the relation between baseline ICH volume and onset-imaging time) and haematoma growth (defined as haematoma enlargement >33% or >6 ml at 24 h)	(1) Early neurological; increase of ≥4 points in the NIHSS score or death 24 h after symptom onset (2) Poor long-term outcome (mRS >2 at 3 months) (3) Mortality at 3 months
Wada et al. [9]	One or more 1- to 2-mm foci of enhancement within the haematoma on CTA source images Spot location within the haematoma and the number of spots were noted Extravasation was defined as enlargement of the contrast density on the immediately proceeding enhanced CT	An increase in hematoma size >30% or >6 ml considered significant enlargement	(1) In-hospital mortality (2) mRS (0–2, 3–5, 6) at 3 months

Table 4. Calculated odds ratio (OR) with 95% CI for HE prediction by the spot sign

Authors	OR	95% CI
Demchuk et al. [11]	5.61	2.98–10.56
Goldstein et al. [10]	13	1.63–103.58
Li et al. [22]	36.51	12.31–108.23
Park et al. [21]	15.75	4.63–53.49
Rodriguez-Luna et al. [23]	3.33	0.93–11.94
Wada et al. [9]	83.33	7.72–899.59

of patients with mRS scores of 0–2, 3–5 and 6, according to the presence or absence of the spot sign.

A number of items on our data extraction form were not available in any, or the majority, of the studies, e.g. prognostic marker data, data on CTA time from admission, second-pass CTA images, number of spot signs, maximum axial dimension and maximum attenuation.

A funnel plot was drawn and visual assessment suggests some possibility of publication bias (see online suppl. appendix 4).

Table 5. Clinical outcomes

Outcome/authors	Prevalence, n/total (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive predictive value, % (95% CI)	Negative predictive value, % (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Accuracy, %
Early clinical deterioration								
Demchuk et al. [11]	36/192 (19%) (14–25)	47 (31–64)	77 (69–83)	32 (20–46)	86 (79–91)	2.05 (1.31–3.21)	0.69 (0.5–0.94)	71
Rodriguez-Luna et al. [23]	18/89 (20%) (13–30)	50 (27–73)	89 (78–95)	53 (28–76)	88 (77–94)	4.44 (1.99–9.87)	0.56 (0.35–0.9)	81
Poor outcome at discharge								
Li et al. [22]	103/139 (74%) (66–81)	26.2 (18–36)	91.7 (74–98)	90 (72–97)	30.3 (22–40)	3.15 (1.02–9.75)	0.80 (0.71–0.91)	43
In-hospital mortality								
Goldstein et al. [10]	26/104 (25%) (17–35)	73 (52–88)	50 (39–61)	32 (21–93)	85 (71–93)	1.46 (1.06–2.02)	0.54 (0.28–1.04)	56
Li et al. [22]	10/139 (7%) (4–13)	60 (27–86)	81.4 (73–87)	20 (8–39)	96.3 (90–99)	3.23 (1.73–6)	0.49 (0.23–1.05)	80
Three-month mortality								
Demchuk et al. [11]	54/211 (26%) (20–32)	43 (30–57)	81 (74–87)	43 (30–58)	80 (73–86)	2.23 (1.43–3.48)	0.71 (0.56–0.9)	71
Li et al. [22]	16/139 (12%) (7–18)	50 (26–74)	82.1 (74–88)	26.7 (13–46)	92.7 (86–97)	2.8 (1.5–5.19)	0.61 (0.37–1)	78
Park et al. [21]	20/110 (18%) (12–27)	40 (20–64)	88 (79–93)	42 (21–66)	87 (78–93)	3.27 (1.51–7.08)	0.68 (0.48–0.98)	79
Rodriguez-Luna et al. [23]	16/89 (18%) (11–28)	36 (16–64)	85 (74–92)	35 (15–61)	86 (75–93)	2.49 (1.2–5.73)	0.74 (0.5–1.1)	76
Wada et al. [9]	7/39 (18%) (8–34)	43 (12–80)	69 (50–83)	23 (6–54)	85 (64–95)	1.37 (0.51–3.72)	0.83 (0.43–1.62)	64
Poor outcome at 3 months								
Li et al. [22]	72/139 (52%) (43–60)	36.1 (25–48)	94 (85–98)	86.7 (68–96)	57.8 (48–67)	6.05 (2.23–16.42)	0.68 (0.57–0.81)	64
Rodriguez-Luna et al. [23]	15/89 (17%) (1–27)	27 (9–55)	82 (71–90)	24 (8–50)	85 (74–92)	1.52 (0.57–4.02)	0.89 (0.65–1.21)	73
Wada et al. [9]	22/39 (56%) (40–72)	41 (21–63)	76 (50–92)	69 (39–90)	50 (30–70)	1.74 (0.64–4.69)	0.77 (0.53–1.13)	56

Table 6. Radiological outcome: accuracy measures for the spot sign in predicting HE

Authors	Prevalence, n/total (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive predictive value, % (95% CI)	Negative predictive value, % (95% CI)	Positive likelihood ratio (95%CI)	Negative likelihood ratio (95%CI)	Accuracy, %
Demchuk et al. [11]	73/228 (32%) (26–39)	51 (39–62)	85 (78–90)	61 (47–73)	78 (71–84)	3.27 (2.13–5.04)	0.58 (0.46–0.74)	74
Goldstein et al. [10]	14/104 (13%) (8–22)	93 (64–100)	50 (39–61)	22 (13–36)	98 (87–100)	1.86 (1.44–2.39)	0.14 (0.02–0.97)	56
Li et al. [22]	32/139 (23%) (16–31)	72 (53–86)	93 (87–97)	77 (57–89)	92 (84–96)	10.99 (5.2–23.22)	0.30 (0.17–0.52)	88
Park et al. [21]	16/110 (15%) (9–23)	63 (36–84)	90 (82–95)	53 (29–75)	93 (86–97)	6.53 (3.15–13.52)	0.41 (0.22–0.78)	86
Rodriguez-Luna et al. [23]	13/89 (15%) (8–24)	38 (15–68)	84 (74–91)	29 (11–56)	89 (79–95)	2.44 (1.03–5.77)	0.73 (0.47–1.13)	78
Wada et al. [9]	11/39 (28%) (16–45)	91 (62–100)	89 (72–96)	77 (50–92)	96 (81–99)	8.50 (2.9–25)	0.10 (0.02–0.7)	90

The variation in odds ratios attributable to heterogeneity was very high ($I^2 = 94.0\%$) in an exploratory test for heterogeneity for the radiological outcome.

Discussion

Summary of Evidence

The systematic review identified 6 cohort studies fulfilling our inclusion and exclusion criteria. Although each study reported an association of the spot sign with HE and poor clinical outcome, the accuracy of this association overall was not measurable, leaving our research question unanswered.

Studies may not be comparable for several reasons. Firstly, the study design was inconsistent. In particular, the retrospective study by Goldstein et al. [10] could have introduced a selection bias, since patients who underwent CTA were able to be included later depending on the treating physician's decision. Similarly, Rodriguez-Luna et al. [23] did not report the reasons why only a subset of patients underwent CTA.

The most striking feature of the selected studies is the use of different definitions, not only for the spot sign, but also for radiological and clinical outcomes.

The presence of contrast extravasation within the haematoma on CTA imaging has been differently classified across studies. Some studies used strictly defined radiological and morphological criteria [11, 21, 22], 1 study did not report any definition [23], and only 1 study differentiated between the terms 'spot sign' and 'contrast extravasation' when the focus of enhancement was seen on CTA source images or on CT images following contrast enhancement, respectively [9]. Since the presence of contrast extravasation might be more sensitive than the presence of the spot sign [19], those terms should not be used interchangeably, especially without specifying the acquisition technique. Lastly, a 'spot sign score' was developed [24] and used in only 1 of the selected papers [22]. In a recently published analysis from the PREDICT study [25], the spot sign score independently predicted HE; however, one of its components alone, the spot number, could improve risk stratification of this event. Furthermore, the pathophysiology of the spot sign is still unclear but could involve a progressive small vessel damage following ICH, as first proposed by Fisher [26] and suggested by a recent study, introducing yet another radiological marker, the 'tail sign', to indicate bleeding in a striate artery in putaminal ICH [27].

HE was also defined differently across studies, using relative (e.g. >30 or 33%) or absolute change (e.g. mostly ≥6 or ≥12·5 ml) in haematoma volume on follow-up CT. The PREDICT study by Demchuk et al. [11] demonstrated that different cut-offs for absolute or relative changes in haematoma volume may not affect the predictive value of HE.

The variety in clinical outcomes is susceptible to outcome reporting bias. Furthermore, definition and analysis of disability (measured with mRS) were often unclear and suboptimal, confirming a recognised limitation of stroke trials [28]. This might be the main limitation of all the selected studies. Indeed, evidence from trials and related meta-analyses investigating recombinant factor VIIa in the setting of spontaneous ICH [29, 30] showed that reducing or even stopping haematoma growth does not necessarily correspond to improving clinical outcome. Although such a result could be explained by inappropriate patient selection, it underlines the importance of identifying appropriate clinical outcomes to reflect expected effects of interventions.

Other quality-related issues could have affected the results. In particular, a sample size calculation was reported by only two groups, with studies potentially being underpowered. Almost no study reported 95% CI of accuracy measures, which should be done for any binomial proportion. When calculated, CI were wide, reflecting relatively small studies. Finally, the choice of candidate variables for univariate and multivariate analyses was not always comprehensive. Ideally, all proposed HE determinants, such as initial haematoma volume [31], time from onset to imaging [32], presence of previous white matter lesions [33, 34], haemorrhage location [35] and presence of cerebral atrophy, the latter independently associated with poor outcome [36], should be included not only for the radiological outcome but also for the clinical outcome.

A risk of bias is also suggested from the funnel plot (online suppl. appendix 4). Given the paucity of studies, only a visual assessment of the direction and distribution of the effect measures of each study on the funnel plot was carried out [17]. Asymmetry could arise from publication bias, since all selected studies reported positive results, poor choice of effect measure or chance. Furthermore, our literature search only identified English language studies, with a potential language bias. In any case, the relatively high variability in the accuracy measures of the spot sign across studies can undermine its role as a prognostic marker [12, 37]. When used for patient selection, a prognostic marker should ideally have a high specificity to minimise the risk of excluding patients who could still benefit from a potentially useful intervention. On the other hand, its use could unnecessarily include patients who have been wrongly recognised as at risk on the basis of a misjudgement of the presence of the spot sign. In this respect, Gazzola et al. [20] reported on spot sign mimics, such as calcifications or pseudo-aneurysms in the setting of tumours, arteriovenous malformations or moyamoya syndrome.

Strengths and Limitations

The present systematic review used recognised standardised methods to search, identify and evaluate eligible studies. However, it has some limitations. Authors were not contacted to obtain the original data for each of the eligible studies, which might have minimised any reporting bias. Furthermore, quality assessment was conducted using a novel tool based on recommendations for tumour marker prognostic studies. Although belonging to a different field, those recommendations had been used by other authors systematically investigating prognostic markers in ischemic stroke [38] and are consistent with expert opinions in the field [39].

Conclusions

In summary, there is no gold standard for the prediction of haematoma growth and poor clinical outcome in spontaneous ICH. Despite its promising performance in single studies, the high variability found in this systematic review does not allow us to conclude that the CTA spot sign is currently a valid prognostic marker, which is in line with the AHA/ASA 2010 recommendations [40]. Incorporating the CTA spot sign in a clinical prediction score including predictors of HE and taking into account oral anti-coagulant agent use could improve the accuracy of risk stratification [41]. Recently, some studies propose a 'dynamic spot sign' using CT perfusion, a quantitative technique which allows a real-time contrast extravasation measurement. The dynamic spot sign seems to be a better prognostic marker than the CTA spot sign with higher sensitivity and predictive value [42–44], however, it needs to be standardised and validated.

In conclusion, further appropriately powered studies, using the best available technique, standardised marker and outcome definitions, and potential combination with other relevant predictors of HE and poor outcome are required before translating study results into clinical practice.

Acknowledgements

We acknowledge Dr. Gabriele Menzel (librarian, Charité University, Berlin) for her assistance in the literature search.

Disclosure Statement

Angela Del Giudice, Delia D'Amico, Jan Sobesky and Ian Wellwood declare no conflicts of interest.

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