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Accuracy of swirl sign for predicting hematoma enlargement in intracerebral hemorrhage: a meta-analysis

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ABSTRACT

Background: Hematoma enlargement happens in about 30% patients with intracerebral hemorrhage, which is reported to be closely correlated with poor prognosis. Swirl sign has been reported to have correlation with hematoma enlargement. This meta-analysis analyzed the accuracy of swirl sign for predicting hematoma enlargement in intracerebral hemorrhage.

Methods: Five databases were searched for potentially eligible literature. Studies were included if they were about the predictive properties of swirl sign for hematoma enlargement in intracerebral hemorrhage. Sensitivity and specificity of swirl sign for hematoma enlargement prediction were pooled. Pooled positive and negative likelihood ratios were also calculated.

Results: Six studies with 2647 patients were finally included in meta-analysis. The pooled sensitivity and specificity of swirl sign were 0.45 (95%CI 0.32–0.59) and 0.79 (95%CI 0.73–0.84), respectively. The pooled positive likelihood ratio of swirl sign was 2.2 (95%CI 1.8–2.5). In contrast, the pooled negative likelihood ratio of swirl sign was 0.69 (95%CI 0.57–0.84).

Conclusions: This meta-analysis suggests that swirl sign has the relatively high specificity for hematoma enlargement prediction in patients with intracerebral hemorrhage.

1. Introduction

Intracerebral hemorrhage brings high mortality and disability [1]. Some important large clinical trials on intracerebral hemorrhage have been done in the past years, but the effective therapy for this disease is not clear until now [2–6]. Hematoma enlargement happens in about 30% patients with intracerebral hemorrhage, which is reported to be closely correlated with poor prognosis [7]. Comparing to other prognostic indicators (for example, initial hematoma volume and location), hematoma enlargement can be prevented if identified early [8]. Although the spot sign is demonstrated as a reliable neuroimaging marker of hematoma enlargement [9–12], it depends on computed tomography angiography (CTA), which is still unobtainable for some patients in the early phase, especially in the remote regions of the developing countries. Some studies have reported some novel markers of hematoma enlargement on non-contrast computed tomography (CT) [13–16]. Swirl sign, which represents the low-density region inside hematoma, has been reported to have correlation with hematoma enlargement in intracerebral hemorrhage [17]. (Fig. 1) However, the results are not consistent in other studies [17,18]. This study is performed to analyze the accuracy of swirl sign for predicting hematoma enlargement in intracerebral hemorrhage based on the current studies.

2. Materials and methods

2.1. Literature search

Literature was searched in two international databases (PubMed and Embase) and three Chinese databases (CNKI, VIP and Wanfang) on July 3, 2018. The search strategy was the combination of the following keywords and their synonyms: intracerebral hemorrhage, swirl sign and hematoma enlargement. We also screened references of relevant articles. Language restriction was not set.

2.2. Study selection

The studies should meet the criteria as follows: (1) Original articles; (2) Intracerebral hemorrhage diagnosed by CT; (3) About swirl sign and

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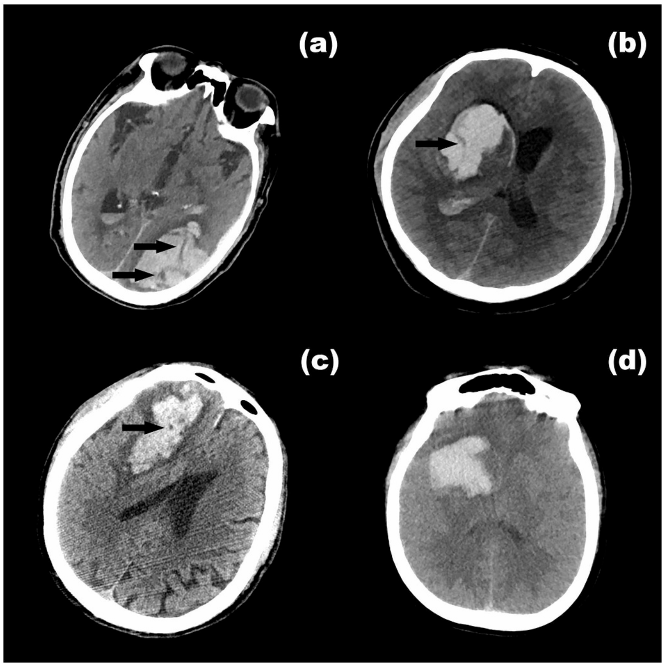

Fig. 1. Illustrative examples of swirl sign in intracerebral hemorrhage: (a)-(c) intracerebral hemorrhage with swirl sign; (d) intracerebral hemorrhage without swirl sign.

hematoma enlargement; (4) sufficient data. The studies would be excluded if: (1) Not original studies; (2) Secondary intracerebral hemorrhage; (3) insufficient data. All studies were assessed by two authors independently. The third author would help to solve any disagreement.

2.3. Data collection and quality assessment

Two authors independently collected the data as follows: first author, publication year, country, number of enrolled patients, male percentage, hematoma enlargement definition, ictus-to-CT time, follow-up CT time, blinding, true positive numbers of patients, true negative numbers of patients, false positive numbers of patients and false negative numbers of patients. Using Quality Assessment of Diagnostic Accuracy Studies (QUADAS), the quality of included studies was independently assessed by two authors. If disagreement occurred, it was solved by discussion with another author.

2.4. Statistical analysis

Calculation of pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and their 95% confidence intervals (CIs) were conducted by bivariate generalized linear mixed model. Heterogeneity among studies was evaluated in Chi-square and Cochran-Q test. Substantial heterogeneity was determined if $I^2 > 50\%$. Summary receiver operator characteristics (SROC) curve was adopted to show the predictive properties of swirl sign for hematoma enlargement in intracerebral hemorrhage. Meta-regression was performed to evaluate the potential influence of possible confounding factors. Assessment of publication bias in this meta-analysis was done with Deeks' funnel plot. If $P < .05$, it was regarded as significant publication bias. Statistical analyses were completed using Stata 14 (Stata Corporation, College Station, TX).

3. Results

3.1. Literature search

A total of 156 records were obtained. After removing duplicated records, there were 88 studies. After checking the titles and abstracts, a total of 11 studies were thought to be potentially eligible studies. After reviewing the full texts, another five studies were excluded including two unrelated studies, one review and two studies only reporting data about outcome. Thus, six studies were finally included. (Fig. 2).

3.2. Features of studies

Table 1 shows the features of included studies in this meta-analysis. The pooled sample size was 2647 in these six studies. The percentage of male ranged from 40.6% to 67.5%. Hematoma enlargement was defined as > 6 mL or > 33% increase in three studies, > 33% increase in one study, increased hematoma volume in one study and > 12.5 mL or > 33% increase in another study. The ictus-to-CT time was different, ranging from 1.9 h to 24 h. The follow-up CT time was between 24 h and 96 h. All studies adopted blinded assessment. Table 2 shows the results of quality assessment.

3.3. Pooled results

The pooled sensitivity of swirl sign for hematoma enlargement prediction was 0.45 (95%CI 0.32–0.59, $I^2 = 90.31\%$) while the pooled specificity of swirl sign was 0.79 (95%CI 0.73–0.84, $I^2 = 82.74\%$). (Fig. 3) In addition, the pooled PLR and NLR were 2.2 (95%CI 1.8–2.5) and 0.69 (95%CI 0.57–0.84), respectively. The pooled area under SROC curve was 0.74 (95%CI 0.69–0.77). (Fig. 4).

3.4. Meta-regression

Meta-regression was conducted according to the diffidence of study design or sample size. Both study design and sample size of included studies influenced specificity significantly. (Table 3).

3.5. Publication bias

No significant publication bias was shown among included studies ($P = .71$). (Fig. 5).

4. Discussion

This meta-analysis is about the accuracy of swirl sign for predicting hematoma enlargement in intracerebral hemorrhage. The pooled sensitivity and specificity of swirl sign for hematoma enlargement prediction were 0.45 and 0.79, respectively. In addition, the pooled area under SROC curve was 0.74. The results of this meta-analysis show that swirl sign has the relatively high specificity for predicting hematoma enlargement, although its sensitivity is low.

Swirl sign, defined as low-density region inside hematoma, was first reported in epidural hematoma and suggested to be related to poor outcome. [19,20] A study by Selariu et al. first discussed swirl sign in intracerebral hemorrhage and found swirl sign was independently related to unfavorable outcome [21]. The correlation between swirl sign and hematoma enlargement was first explored in the study by Conner et al. [22] In that study, its sensitivity was 0.67 and specificity was 0.62 [22]. In another study by Boulouis et al., this imaging marker was correlated with hematoma enlargement in univariate analysis, but no significant association was found in multivariable analysis [15]. Morotti et al. analyzed ATACH-2 cohort and suggested the sensitivity and specificity of swirl sign were 0.33 and 0.83, respectively [23]. In the

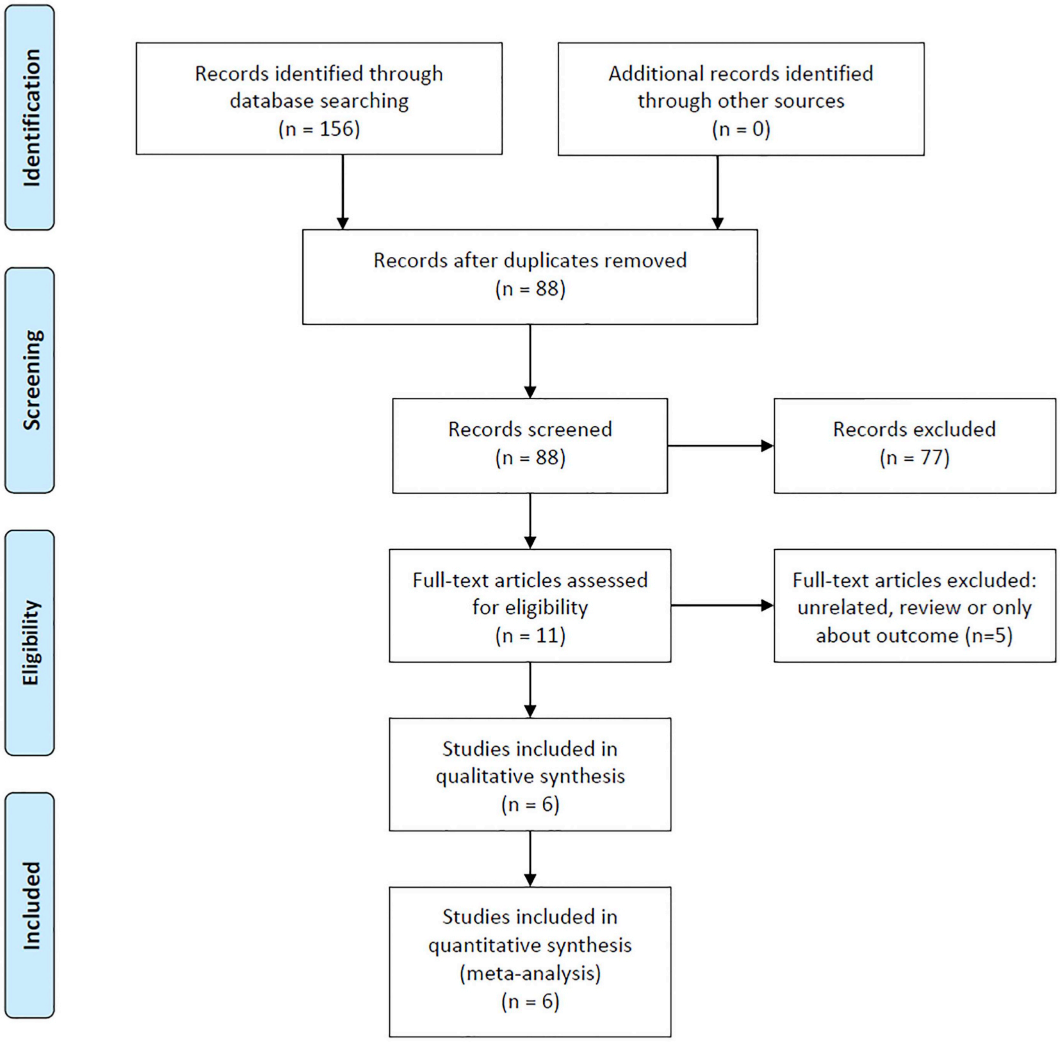

Fig. 2. Flow diagram of study selection.

Table 1
Features of included studies.

Study	Year	Country	Study design	Sample size	Male, %	HE definition	Ictus-to-CT time	Follow-up CT time	Blinding
Connor	2015	Canada	Retrospective	71	64.8%	> 6 mL or > 33%	Median 1.9 h	24 h	Yes
Boulouis	2016	USA	Retrospective	1029	45.1%	> 6 mL or > 33%	Development cohort: Median 4.9 h; Replication cohort: median 3.2 h	48 h	Yes
Morotti	2017	International	Prospective	869	61.9%	> 33%	4.5 h	24 h	Yes
Ng	2018	Australia	Retrospective	212	40.6%	Increased hematoma volume	Median 4.5 h	96 h	Yes
Xiong	2018	China	Prospective	200	67.5%	> 12.5 mL or > 33%	6 h	24 h	Yes
Huang	2018	China	Retrospective	266	65.0%	> 6 mL or > 33%	24 h	24 h	Yes

HE = Hematoma enlargement; CT = Computed tomography.

study by Xiong et al., the sensitivity of swirl sign was 0.47 and the specificity was 0.71 [18]. The study by Ng et al. demonstrated that swirl sign in intracerebral hemorrhage was independently related to hematoma enlargement [17]. In a recent study by Huang et al., the sensitivity of swirl sign was 0.25 and the specificity was 0.85 [24]. In this meta-analysis, although pooled sensitivity of swirl sign was only 0.45, its pooled specificity was 0.79. Combining the results of previous original studies and this meta-analysis, we can find that swirl sign is not sensitive, but it is a relatively specific neuroimaging marker for hematoma enlargement prediction. Patients with positive swirl sign can have high risk of hematoma enlargement and early treatment targeted at hematoma enlargement may improve their outcome. Moreover, swirl sign is defined based on non-contrast CT, which can be easily used at the early phase of intracerebral hemorrhage. This marker on non-contrast CT can be helpful for screening patients at high risk of hematoma enlargement in future clinical trials. Furthermore, since swirl sign has relatively high specificity for predicting hematoma enlargement, this marker should be investigated when developing a comprehensive predictive score based on non-contrast CT markers in the future.

Besides swirl sign, several different predictors based on hematoma

Table 2
Quality evaluation using QUADAS (Quality Assessment of Diagnostic Accuracy Studies).

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Connor (2015)	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Boulouis (2016)	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Morotti (2017)	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ng (2018)	Y	Y	Y	N/A	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Xiong (2018)	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Huang (2018)	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y, satisfied; N, not satisfied; N/A, not applicable.
QUADAS criteria: 1. Was the spectrum of patients representative of the patients who will receive the test in practice? 2. Were selection criteria clearly described? 3. Is the reference standard likely to correctly classify the target condition? 4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests? 5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis? 6. Did patients receive the same reference standard regardless of the index test result? 7. Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard)? 8. Was the execution of the index test described in sufficient detail to permit replication of the test? 9. Was the execution of the reference standard described in sufficient detail to permit its replication? 10. Were the index test results interpreted without knowledge of the results of the reference standard? 11. Were the reference standard results interpreted without knowledge of the results of the index test 12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? 13. Were uninterpretable/intermediate test results reported? 14. Were withdrawals from the study explained?

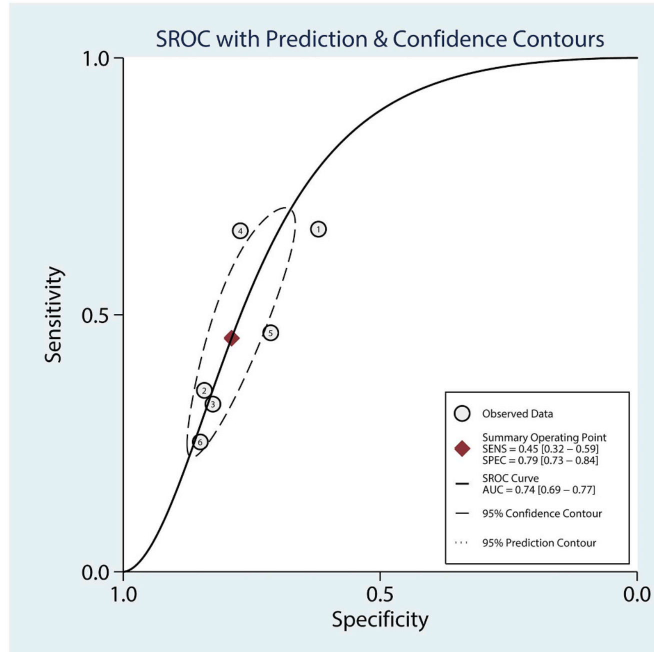

Fig. 4. Summary receiver operating characteristics curve.

density for hematoma enlargement have been defined in recent years. In a previous study by Barras et al., the hematoma density was evaluated using a five-point scale and heterogeneous density was suggested

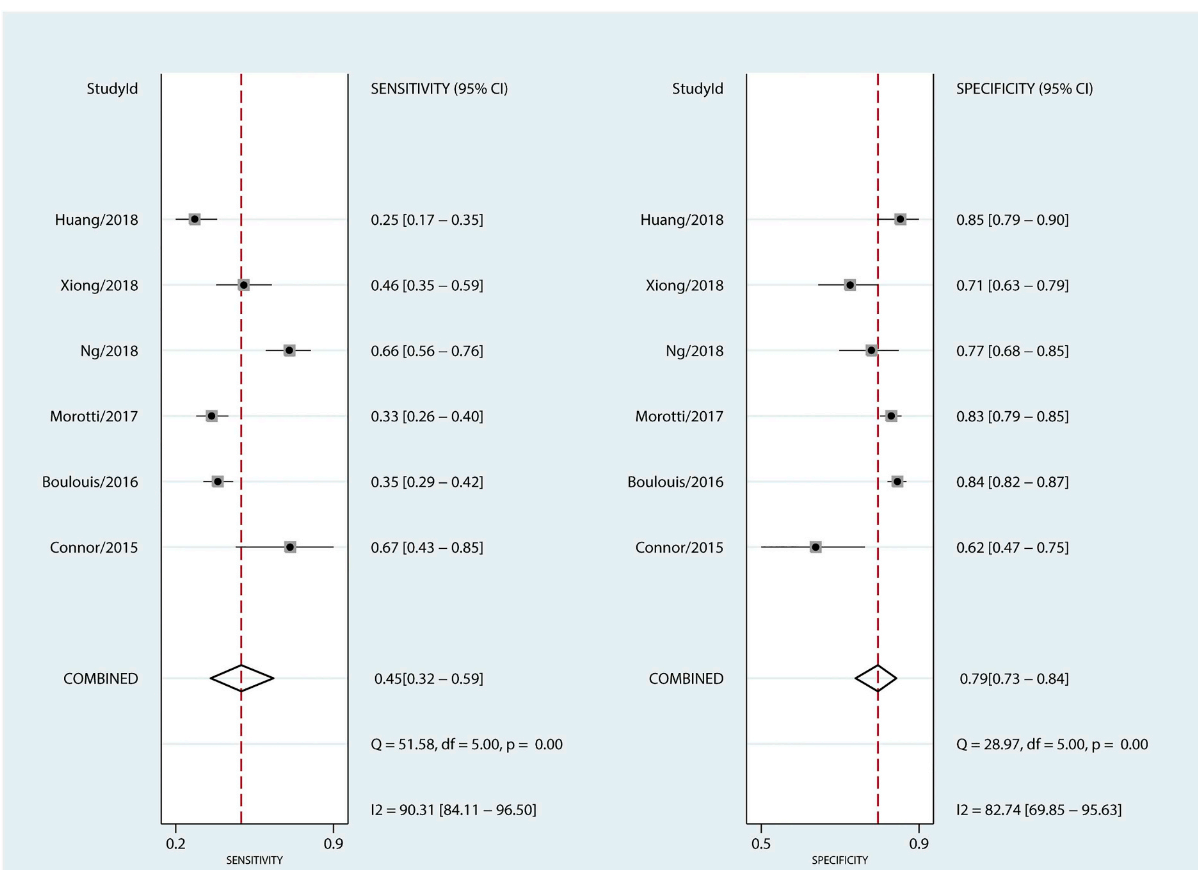

Fig. 3. Forest plots for pooled sensitivity and specificity.

Table 3
Meta-regression.

Parameter	n	Sensitivity(95%CI)	P	Specificity(95%CI)	P
Sample size			0.46		0.01
≥300	2	0.34 (0.16–0.52)		0.83 (0.78–0.89)	
< 300	4	0.51 (0.36–0.67)		0.76 (0.69–0.82)	
Study design			0.53		0.02
Retrospective	4	0.49 (0.31–0.66)		0.79 (0.72–0.86)	
Prospective	2	0.40 (0.17–0.63)		0.79 (0.69–0.88)	

n = Number of studies; CI = Confidence interval.

to be independently related to hematoma enlargement. However, meta-analysis showed that heterogenous density had relatively low accuracy [25]. Li et al. first defined blend sign as mixed low and high density regions, and suggested that it was a specific marker for hematoma enlargement prediction [14]. Black hole sign was also defined by Li et al. and was shown to be an reliable indicator for hematoma enlargement [16]. In addition, Boulouis et al. defined another new predictor, hypodensities, which was also independently related to hematoma enlargement [15]. In a previous meta-analysis by Zhang et al., predictors on non-contrast CT describing heterogeneous density were significantly correlated with hematoma enlargement in intracerebral hemorrhage [26]. Although all these predictors above are based on the density of ICH, their definitions and criteria are still different. Thus, further studies are needed to compare them in larger cohort to determine the optimal marker based on hematoma density for predicting hematoma enlargement.

Except the predictors based on hematoma density, several novel non-contrast CT predictors related to hematoma margin or shape were reported recently. Blacquiere et al.'s study showed that irregular shape was independently related to hematoma enlargement [27]. However, meta-analysis suggested that both sensitivity and specificity of irregular shape were relatively low [25]. Satellite sign, defined as an independent small hematoma near main hematoma, was first reported by Shimoda et al. and was significantly correlated with poor prognosis in intracerebral hemorrhage [28]. A recent study suggested that satellite sign was also a marker for hematoma enlargement [29]. Another new predictor, island sign, which represented extremely irregular hematoma and was shown to be significantly correlated with hematoma enlargement [30]. Further studies with larger sample size should confirm the roles of these shape-related markers in predicting hematoma enlargement and compared them to those predictors based on hematoma density. Moreover, to improve the accuracy of non-contrast CT tool for predicting hematoma enlargement, a comprehensive predictive score including multiple markers should be developed.

This meta-analysis has some limitations. First, only six studies were finally included, which might impact the accuracy of the results. Second, the definitions of swirl sign were slightly different in these studies. In five studies [15,18,22–24], the definition of swirl sign followed the study by Selariu et al. [21]. In contrast, swirl sign should be a hypodense area with 30–50 HU in hyperdense area in Ng et al.'s study [17]. The variant definitions in different studies could cause bias of the results. Third, heterogeneity among included studies was high, which could be related to different sample sizes, study designs, definitions for hematoma enlargement, ictus-to-CT time and follow-up CT time. Moreover, meta-regression showed confounding factors significantly influenced the results. Thus, the pooled results in this meta-analysis should be used cautiously. More studies about swirl sign and hematoma enlargement are still needed to strengthen the current evidences.

In conclusion, this meta-analysis suggests that swirl sign on non-contrast CT has relatively high specificity for hematoma enlargement prediction in intracerebral hemorrhage.

Conflicts of interest

None.

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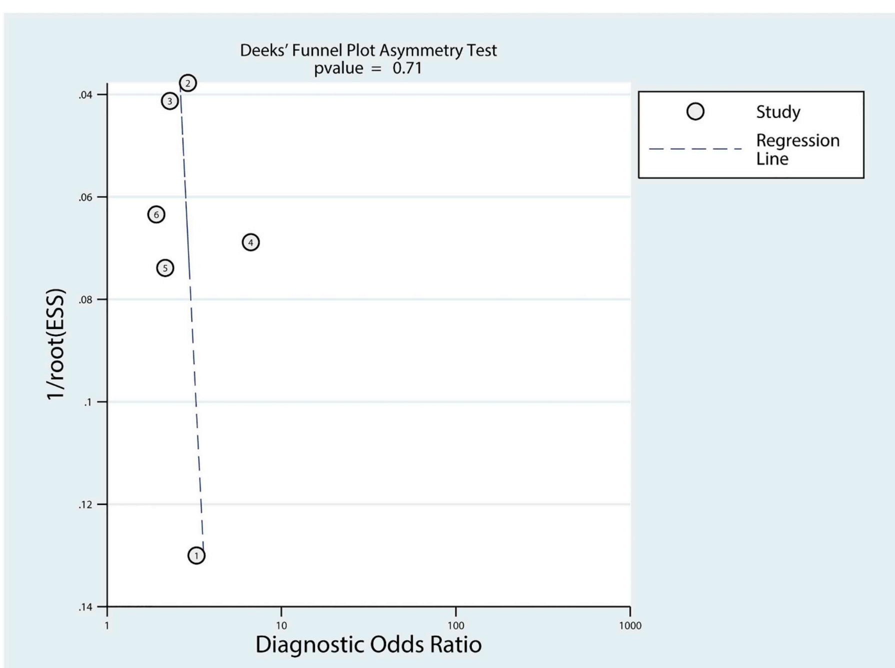

Fig. 5. Deeks' funnel plot.

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