



Perfusion CT for prediction of hemorrhagic transformation in acute ischemic stroke: a systematic review and meta-analysis

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Abstract

Objective To investigate the diagnostic performance of perfusion CT for prediction of hemorrhagic transformation in acute ischemic stroke.

Methods A computerized literature search of Ovid MEDLINE and EMBASE was conducted up to October 29, 2018. Search terms included *acute ischemic stroke*, *hemorrhagic transformation*, and *perfusion CT*. Studies assessing the diagnostic performance of perfusion CT for prediction of hemorrhagic transformation in acute ischemic stroke were included. Two reviewers independently evaluated the eligibility of the studies. A bivariate random effects model was used to calculate the pooled sensitivity and pooled specificity. Multiple subgroup analyses were performed.

Results Fifteen original articles with a total of 1134 patients were included. High blood-brain barrier permeability and hypoperfusion status derived from perfusion CT are associated with hemorrhagic transformation. The pooled sensitivity and specificity were 84% (95% CI, 71–91%) and 74% (95% CI, 67–81%), respectively. The area under the hierarchical summary receiver operating characteristic curve was 0.84 (95% CI, 0.81–0.87). The Higgins I^2 statistic demonstrated that heterogeneity was present in the sensitivity ($I^2 = 80.21%$) and specificity ($I^2 = 85.94%$).

Conclusion Although various perfusion CT parameters have been used across studies, the current evidence supports the use of perfusion CT to predict hemorrhagic transformation in acute ischemic stroke.

Key Points

- High blood-brain barrier permeability and hypoperfusion status derived from perfusion CT were associated with hemorrhagic transformation.
- Perfusion CT has moderate diagnostic performance for the prediction of hemorrhagic transformation in acute ischemic stroke.
- The pooled sensitivity was 84%, and the pooled specificity was 74%.

Keywords Stroke · Hemorrhage · Perfusion

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Abbreviations

CI	Confidence interval
CT	Computed tomography
DOR	Diagnostic odds ratio
HSROC	Hierarchical summary receiver operating characteristic
MRI	Magnetic resonance imaging
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2

Introduction

Hemorrhagic transformation is a lethal complication of reperfusion treatment in acute ischemic stroke and is associated with increased mortality and a poor clinical outcome [1]. Several factors are known to be associated with hemorrhagic transformation, including the etiology of stroke, NIHSS score, age, and the use of recombinant tissue plasminogen activator (tPA) [2–4]. In addition, imaging modalities including non-contrast computed tomography (CT) [5] and conventional or advanced magnetic resonance imaging (MRI) [6, 7] have been investigated for the prediction of hemorrhagic transformation.

Over the last decade, many researchers have investigated the role of perfusion CT for predicting hemorrhagic transformation in acute ischemic stroke [8–22]. Various perfusion CT parameters have revealed promising results in the prediction of hemorrhagic transformation. If perfusion CT can yield additional information in terms of the risk of hemorrhagic transformation, it should be of further help in selecting candidates for thrombolytic therapy. Therefore, if perfusion CT can be used for the imaging prediction of hemorrhagic transformation, it will be a valuable modality for clinical decision-making.

However, the diagnostic performance of perfusion CT for prediction of hemorrhagic transformation in acute ischemic stroke has not yet been systematically evaluated. In addition, if heterogeneity is present in the diagnostic use of perfusion CT, any covariates affecting its diagnostic performance should be identified. Therefore, this systematic review and meta-analysis aimed to investigate the diagnostic performance of perfusion CT for prediction of hemorrhagic transformation in acute ischemic stroke.

Materials and methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23].

Literature search

A computerized literature search of Ovid MEDLINE and EMBASE was conducted to find original articles investigating the diagnostic performance of perfusion CT for prediction of hemorrhagic transformation in acute ischemic stroke published up to October 29, 2018. The search terms were as follows: ((acute ischemic stroke) OR (“cerebral ischemia”) OR (“cerebrovascular ischemia”) OR (stroke)) AND (“hemorrhagic transformation”) OR (“haemorrhagic transformation”) OR (“parenchymal hematoma”)) AND (“computed tomography perfusion”) OR (“CT perfusion”) OR (“perfusion computed tomography”) OR (“perfusion CT”). The search was not limited by starting date, language, or whether studies were human- or animal-based. Any additional articles identified were screened to expand the search.

Eligibility criteria

Studies or subsets of studies were included if all of the following inclusion criteria were satisfied: (1) patients presented with stroke symptoms; (2) patients underwent emergency perfusion CT before treatment; (3) follow-up CT or MRI (including gradient-echo T2-weighted imaging) to detect hemorrhagic transformation was completed; and (4) there were sufficient data for the reconstruction of 2×2 tables for determination of the diagnostic performance of perfusion CT for prediction of hemorrhagic transformation in acute ischemic stroke.

Studies or subsets of studies were excluded if any of the following exclusion criteria were satisfied: (1) conference abstracts; (2) review articles; (3) case reports including fewer than 10 patients; (4) reports just defining a study protocol; (5) insufficient data to reconstruct a 2×2 table; (6) studies not in the English language; and (7) studies with a partially overlapping patient cohort. Authors of articles not providing sufficient data for the reconstruction of 2×2 tables were contacted for the provision of further data.

Data extraction and quality assessment

A standardized form was used to extract the following data from the included studies. (1) Study characteristics: affiliation, patient recruitment period, prospective or retrospective design, case-control study, consecutive or non-consecutive enrollment, reference standard, interval between CT perfusion and follow-up CT or MRI, number of readers, reader experience, and blindness of readers to clinical or reference standard. (2) Patient characteristics: total number of patients, number of patients with hemorrhagic transformation, male to female ratio, mean age, and symptom onsets. (3) Technical characteristics of perfusion CT: number of detectors, vendor, model, peak kilovoltage, milliampere, section thickness, z-axis

coverage, contrast agent type, dose of contrast agent, injection rate of contrast agent, software for CT perfusion, CT perfusion parameters, and cutoff values for diagnosis of hemorrhagic transformation.

Quality assessment was performed according to the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [24]. The literature search, literature selection, data extraction, and quality assessment were performed independently by two reviewers (C.H.S. and S.C.J.).

Data synthesis and analysis

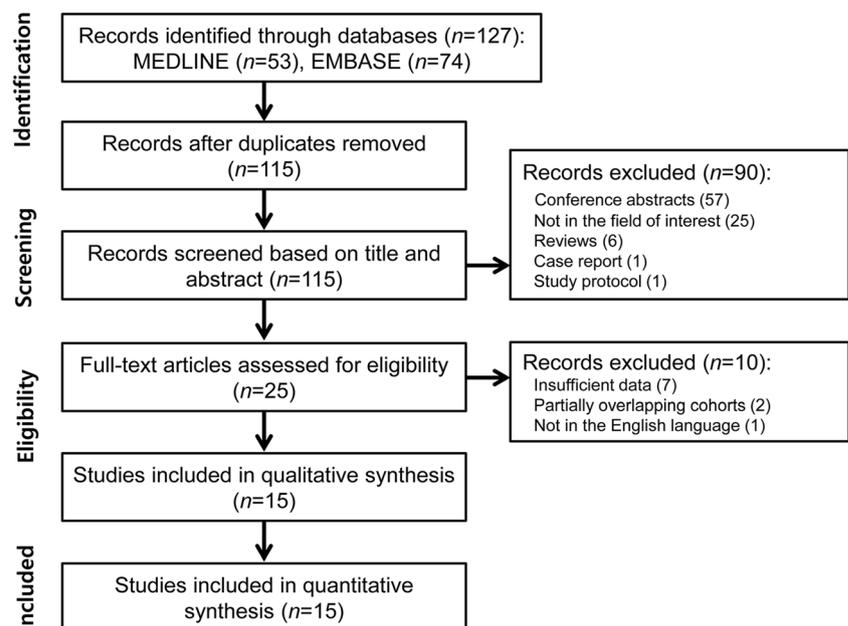
For the 2×2 tables, the results with the highest diagnostic performance were used if multiple CT perfusion parameters were separately assessed. A bivariate random effects model was used to calculate the pooled sensitivity and pooled specificity and their 95% confidence intervals (CIs) [25–29]. The diagnostic odds ratio (DOR), which was defined as the odds of having a positive perfusion CT result in patients with hemorrhagic transformation compared with the odds of having a positive perfusion CT result in patients without hemorrhagic transformation, was also obtained. For graphical presentation, a coupled forest plot was performed and a hierarchical summary receiver operating characteristic (HSROC) curve with 95% confidence and prediction regions was plotted. Deeks' funnel plot was also performed to test for publication bias, with statistical significance being assessed using Deeks' asymmetry test [30].

Study heterogeneity was evaluated as follows. (1) Cochran's Q -test with $p < 0.05$ indicating the presence of

heterogeneity; (2) Higgins inconsistency index (I^2) test with $I^2 > 50\%$ indicating the presence of heterogeneity [31]; (3) visual assessment of the difference between the 95% confidence and prediction regions in the HSROC curve with a large difference indicating heterogeneity; (4) visual assessment of the coupled forest plot for the presence of a threshold effect (a positive correlation between sensitivity and false positive rate among the selected studies); and (5) a Spearman correlation coefficient > 0.6 indicating a threshold effect [32]. Multiple subgroup analyses were performed as follows: (1) studies using permeability-related parameters, (2) other traditional parameters, (3) prospective studies, (4) retrospective studies, (5) consecutive enrollment, (6) non-consecutive enrollment, (7) hemorrhagic transformation $< 68.6\%$ (median value of the included studies), (8) hemorrhagic transformation $\geq 68.6\%$, (9) number of readers ($n = 1$), (10) number of readers ($n \geq 2$), (11) reader blindness to the reference standard, (12) studies including patients who underwent intravenous (IV) tPA, (13) studies including patients who underwent IV tPA or intraarterial (IA) tPA, and (14) studies including patients who underwent mechanical thrombectomy.

Statistical analysis was performed by one of the authors (C.H.S., with 5 years of experience in performing systematic reviews and meta-analysis) using the "Metandi" and "Midas" modules in Stata 15.0 (StataCorp, College Station, TX) and the "Mada" package in R version 3.4.1 (R Foundation for Statistical Computing). $p < 0.05$ was regarded as indicating statistical significance.

Fig. 1 Flow diagram of the literature selection process



Results

Literature search

The detailed literature selection process is shown in Fig. 1. The systematic search found 127 articles. After removal of 12 duplicate articles, screening of the abstracts of the 90 remaining articles was performed. Ninety articles were excluded as follows: 57 conference abstracts, 25 articles that were not in the field of interest, 6 reviews, 1 case report, and 1 study protocol. Full-text reviews of the remaining 25 potentially eligible articles were then performed. Ten articles were excluded as follows: seven articles with insufficient data to reconstruct 2×2 tables [33–39], two articles with a partially overlapping cohort [40, 41], and one article not in the English language [42]. Finally, 15 original articles evaluating the diagnostic performance of perfusion CT for prediction of hemorrhagic transformation in acute ischemic stroke, with a total of 1134 patients, were included [8–22].

Characteristics of the included studies

The patient and study characteristics are shown in Table 1. Five studies were of a prospective design [8, 9, 12, 17, 18], and nine were retrospective [10, 11, 13–16, 19, 20, 22]. All included studies used follow-up non-contrast CT or MRI (including gradient-echo T2-weighted MR) as a reference standard. Hemorrhagic transformation categorized as hemorrhagic infarction and parenchymal hematoma was evaluated according to the European Cooperative Acute Stroke Study [4]. Patients (15–100% of patients) underwent only IV tPA in 6 studies [11, 13, 17–19, 21] and IV tPA or IA tPA in 3 studies [8, 14, 15]. A small portion of patients (7–52% of patients) underwent mechanical thrombectomy in 5 studies (Table 1) [9, 12, 16, 20, 22].

The detailed perfusion CT characteristics are shown in Table 2. Eleven of 15 studies (73%) used CT scanners with 64 or more slices [8, 10–13, 17–22], and two studies used 16 slice CT scanners [14, 15]. Eleven of 15 studies (73%) used 80 kVp [8–11, 13–16, 19, 20, 22], whereas the milliamperage values varied across the studies. In terms of contrast agent, all included studies used 35–50 ml of iodinated contrast agent and injection rates of 4–7 ml/s. Only four studies reported the radiation dose of the perfusion CT [9, 10, 20, 22], with these radiation doses ranging from 2.7 to 7.9 mSv.

Quality assessment

The quality of the included studies was considered moderate, as 14 of 15 studies scored more than 4 out of 7 in the QUADAS-2 domains (Supplementary Fig. 1). In the patient selection domain, two studies were regarded as having an unclear risk of bias because of non-consecutive enrollment

[11, 15], and one study was regarded as having a high risk of bias due to it being a case-control design [9]. In the index test domain, six studies were regarded as having an unclear risk of bias as it was unclear whether perfusion CT was performed blinded to the reference standard [9–12, 21, 22]. In the reference standard domain, seven studies were regarded as having an unclear risk of bias as it was unclear whether evaluation of the reference standard was performed blinded to perfusion CT [9–11, 14, 16, 21, 22]. In the flow and timing domain, four studies were regarded as having an unclear risk of bias because the time intervals between perfusion CT and the reference standard were not mentioned [10, 11, 15, 22]. There were no concerns about the applicability of any of the included studies.

Perfusion CT parameters predicting hemorrhagic transformation: a systematic review

Various CT perfusion parameters have been used to predict hemorrhagic transformation in acute ischemic stroke. Nine of 15 studies (60%) used permeability-related parameters to predict hemorrhagic transformation [8–10, 12–14, 17, 18, 22], with five of these studies (33%) using permeability-surface area product (PS) [8, 9, 14, 17, 22]. These five studies consistently showed that the PS value of the hemorrhagic transformation group was significantly higher than that of the non-hemorrhagic transformation group. Three of 15 studies (20%) used blood-brain barrier permeability (K^{trans}), and these also showed high permeability for the hemorrhagic transformation group compared with the non-hemorrhagic transformation group [10, 12, 13]. One study used the size of the region showing high permeability on perfusion CT as a parameter [18].

Six of 15 studies (40%) used traditional perfusion CT parameters, with three studies (20%) using cerebral blood volume (CBV) [11, 15, 16], one using relative cerebral blood flow (CBF) [20], one using Tmax [21], and one using time-to-peak (TTP) map defect [19]. These studies showed lower CBV [11, 15], lower CBF [20], or prolonged Tmax [21] for the hemorrhagic transformation group in comparison with the non-hemorrhagic transformation group.

Diagnostic performance of perfusion CT for prediction of hemorrhagic transformation: a meta-analysis

The sensitivities and specificities of the individual included studies ranged from 44 to 100% and from 41 to 94%, respectively. The pooled sensitivity and specificity for the diagnostic performance of perfusion CT for prediction of hemorrhagic transformation were 84% (95% CI, 71–91%) and 74% (95% CI, 67–81%; Fig. 2), respectively. The estimated positive predictive value was 46% and the estimated negative predictive value was 77%. The DOR was 15 (95% CI, 7–31), and the

Table 1 Study and patient characteristics of the included studies

Author (year of publication)	Institution	Duration of patient recruitment	No. of patients (n)	Hemorrhagic transformation (n)	Non-hemorrhagic transformation (n, %)	Male:female	Mean age (years)	Study design	Consecutive enrollment	Treatment	Reference standard
Aviv RI et al [8] (2009)	Sunnybrook Health Science Centre, Canada	2006.1–2007.10	41	23	18 (43.9)	26:15	70.3	Prospective	Yes	IV tPA (n = 20), IA tPA (n = 2)	Follow-up non-contrast CT or MRI (GRE) at 3 days
Bennink E et al [9] (2015)	University Medical Center Utrecht, The Netherlands	2009.5–2013.7	60	20	40 (66.7)	36:24	69	Prospective	Yes	IV tPA (n = 55), IA tPA or MT (n = 4)	Follow-up non-contrast CT at 3 days
Hom J et al [10] (2011)	University of California San Francisco, USA	2006.7–2009.4	32	6	26 (81.3)	NA	Median 72	Retrospective	Yes	NA	Follow-up non-contrast CT or MRI
Jain AR et al [11] (2013)	University of Rochester Medical Center, USA	2009.7–2010.2	83	16	67 (80.7)	46:37	72	Retrospective	NA	IV tPA (n = 23)	Follow-up non-contrast CT or MRI
Kim T et al [12] (2018)	Incheon St. Mary's Hospital, South Korea	2013.5–2015.4	46	15	31 (67.4)	25:21	66	Prospective	Yes	IV tPA (n = 34), MT (n = 24)	Follow-up non-contrast CT or MRI (GRE) at 1 day
Li Y et al [13] (2017)	Military General Hospital of Beijing PLA, Southwest Hospital, Changhai Hospital, China	2011.1–2014.1	106	48	58 (54.7)	59:47	65.3	Retrospective	Yes	IV tPA (n = 106)	Follow-up MRI (GRE) at 3 days
Lin K et al [14] (2007)	New York Presbyterian Hospital, USA	2004.1–2006.4	50	6	44 (88.0)	23:27	NA	Retrospective	Yes	IV tPA (n = 16), IA tPA (n = 2)	Follow-up non-contrast CT or MRI at 3 days
Lin K et al [15] (2012)	New York Presbyterian Hospital, USA	NA	84	22	62 (73.8)	40:44	70.6	Retrospective	NA	IV or IA tPA (n = 39)	Follow-up non-contrast CT or MRI (GRE)
Liu L et al [16] (2017)	Beth Israel Deaconess Medical Center, USA	2008.1–2013.9	52	18	34 (65.4)	19:33	75	Retrospective	Yes	IV tPA (n = 15), IV tPA and MT (n = 7), IV and IA tPA (n = 2)	Follow-up MRI (GRE) within 3 days
Ozkul-Wermester O et al [17] (2014)	Rouen University Hospital, France	2009.6–2010.12	86	27	59 (68.6)	48:38	64.6	Prospective	Yes	IV tPA (n = 31)	Follow-up MRI (GRE) at 5–7 days
Puig J et al [18] (2017)	Hospital Universitari Dr. Josep Trueta, Spain	2012.10–2016.6	156	37	119 (76.3)	78:78	75.3	Prospective	Yes	IV tPA (n = 156)	Follow-up non-contrast CT at 1 day
Shinoyama M et al [19] (2013)	Nakamura Memorial Hospital, Japan	2010.1–2010.9	68	34	34 (50.0)	41:27	72.9	Retrospective	Yes	IV tPA (n = 10)	Follow-up non-contrast CT or MRI (GRE) within 14 days
		2008.4–2009.5	96	22	74 (77.1)	60:36	67.1	Retrospective	Yes		

Table 1 (continued)

Author (year of publication)	Institution	Duration of patient recruitment	No. of patients (n)	Hemorrhagic transformation (n)	Non-hemorrhagic transformation (n, %)	Male:female (n)	Mean age (years)	Study design	Consecutive enrollment	Treatment	Reference standard
Souza LC et al [20] (2012)	Massachusetts General Hospital, USA									IV tPA (n = 41), MT (n = 20), IA tPA (n = 3)	Follow-up non-contrast CT or MRI at 5 days
Yassi N et al [21] (2013)	John Hunter Hospital, Australia	2009.12–2012.7	132	14	118 (89.4)	102:30	74	NA	Yes	IV tPA (n = 70)	Follow-up non-contrast CT or MRI within 10 days
Yen P et al [22] (2016)	Queen Elizabeth II Health Sciences Centre, Canada	5 months	42	15	27 (64.3)	19:23	70	Retrospective	Yes	IV tPA (n = 38), IV tPA and MT (n = 5)	Follow-up non-contrast CT or MRI

NA not available, IV intravenous, tPA tissue plasminogen activator, IA intraarterial, MT mechanical thrombectomy, GRE gradient-echo T2-weighted MR

area under the HSROC curve was 0.84 (95% CI, 0.81–0.87; Fig. 3). Deeks' funnel plot revealed a high likelihood of publication bias ($p = 0.01$; Supplementary Fig. 2).

The Q -test demonstrated that heterogeneity was present across the studies ($Q = 56.398$, $p < 0.001$), and the Higgins I^2 statistic demonstrated the presence of heterogeneity in both the sensitivity ($I^2 = 80.21\%$) and specificity ($I^2 = 85.94\%$). There was a large difference between the 95% confidence and prediction regions in the HSROC curve, which also indicates the presence of heterogeneity across the studies (Fig. 3). Visual assessment of the coupled forest plot of sensitivity and specificity did not reveal a threshold effect (Fig. 2), and neither did the Spearman correlation coefficient between the sensitivity and false positive rate (0.359 (95% CI, -0.187 to 0.736)).

Subgroup analysis

In the subgroup analysis, studies using permeability-related parameters showed similar sensitivity (78% (95% CI, 63–88%)) and specificity (76% (95% CI, 65–84%)), with the area under the HSROC curve being 0.83 (95% CI, 0.80–0.86) (Supplementary Table 1). Heterogeneity was present in the sensitivity ($I^2 = 76.76\%$) and specificity ($I^2 = 89.79\%$). The studies using other traditional parameters showed a sensitivity of 90% (95% CI, 68–97%) and a specificity of 72% (95% CI, 60–82%), with an area under the HSROC curve of 0.85 (95% CI, 0.81–0.87). Heterogeneity was present in the sensitivity ($I^2 = 83.89\%$) and specificity ($I^2 = 80.52\%$). There were no statistically significant differences between the sensitivity and specificity of permeability-related parameters and other traditional parameters ($p = 0.92$).

The studies including patients who underwent IV tPA (15–100% of patients) showed a sensitivity of 90% (95% CI, 61–98%) and a specificity of 67% (95% CI, 55–78%). The studies including patients who underwent mechanical thrombectomy (7–52% of patients) showed a sensitivity of 89% (95% CI, 70–100%) and a specificity of 86% (95% CI, 76–96%).

Discussion

This study demonstrates that high blood-brain barrier permeability and hypoperfusion status derived from perfusion CT are associated with hemorrhagic transformation. Perfusion CT has moderate diagnostic performance in the prediction of hemorrhagic transformation in acute ischemic stroke, with a pooled sensitivity of 84% (95% CI, 71–91%) and pooled specificity of 74% (95% CI, 67–81%). The area under the HSROC curve was 0.84 (95% CI, 0.81–0.87). Study heterogeneity was present in both sensitivity ($I^2 = 80.21\%$) and specificity ($I^2 = 85.94\%$). Although various perfusion CT parameters were used across the studies, the current evidence

Table 2 Perfusion CT characteristics of the included studies

Author (year of publication)	Slices	Vendor	Scanner	kVp	mA	Section thickness	Contrast	Dose	Injection rate	Parameter	Cutoff
Permeability-related parameters											
Aviv RI et al [8] (2009)	64	GE Healthcare	VCT	80	190	5	Iohexol	0.5 ml/kg (max 50)	4 ml/s	PS	0.23 ml/100 g/min
Lin K et al [14] (2007)	16	Siemens Healthcare	Sensation	80	200	NA	Iohexol	50 ml	4–5 ml/s	PS	5.1625 ml/100 g/min
Ozkul-Wermester O et al [17] (2014)	64	GE Healthcare	Lightspeed	NA	NA	NA	Iodinated contrast agent	47 ml	4 ml/s	PS	0.84 ml/100 g/min
Bennink E et al [9] (2015)	40–256	NA	NA	80	125–150	0.625–1.25	Nonionic contrast agent	40 ml	6 ml/s	Relative PS	1.12
Yen P et al [22] (2016)	128	Siemens Healthcare	Sensation Definition	80	100	5	Iopamidol	40 ml	5 ml/s	Relative PS	1.3
Puig J et al [18] (2017)	128	GE Healthcare	Ingenuity	100	100	10	Iopromide	50 ml	5 ml/s	High-permeability region size on perfusion CT	29.42 cm ²
Hom J et al [10] (2011)	64	NA	NA	80	100	NA	Iohexol	40 ml	5 ml/s	K^{trans}	7 ml/100 g/min
Kim T et al [12] (2018)	64	NA	NA	NA	NA	NA	NA	NA	NA	K^{trans}	7 ml/100 g/min
Li Y et al [13] (2017)	64	GE Healthcare	Discovery CT750 HD	80	100	NA	Iohexol	40 ml	4 ml/s	K^{trans}	0.35 ml/100 g/min
Other parameters											
Jain AR et al [11] (2013)	64	Philips Healthcare	Brilliance	80	150	5	Ioversol	50 ml	5 ml/s	rCBV	1.09
Lin K et al [15] (2012)	16	GE Healthcare	Lightspeed	80	200	4	Nonionic contrast agent	50 ml	5 ml/s	CBV	5
Liu L et al [16] (2017)	NA	NA	NA	80	500	5	Nonionic contrast agent	40 ml	4 ml/s	CBV-ASPECTS	0–7
Souza LC et al [20] (2012)	64	GE Healthcare	Lightspeed 64	80	500	5	Nonionic contrast agent	35 ml	7 ml/s	rCBF	0.48
Shinoyama M et al [19] (2013)	128	Siemens Healthcare	SOMATOM Definition AS+	80	180	5	Iohexol	40 ml	5 ml/s	TTP map defect	Presence
Yassi N et al [21] (2013)	320 or 64	Toshiba Medical Systems or Philips Healthcare	Aquilion One or Brilliance	NA	NA	5 or 10	Iopromide	40 ml	6 ml/s	Tmax	14

NA not available, PS permeability-surface area product, CBV cerebral blood volume, ASPECTS Alberta Stroke Program Early CT Score, CBF cerebral blood flow

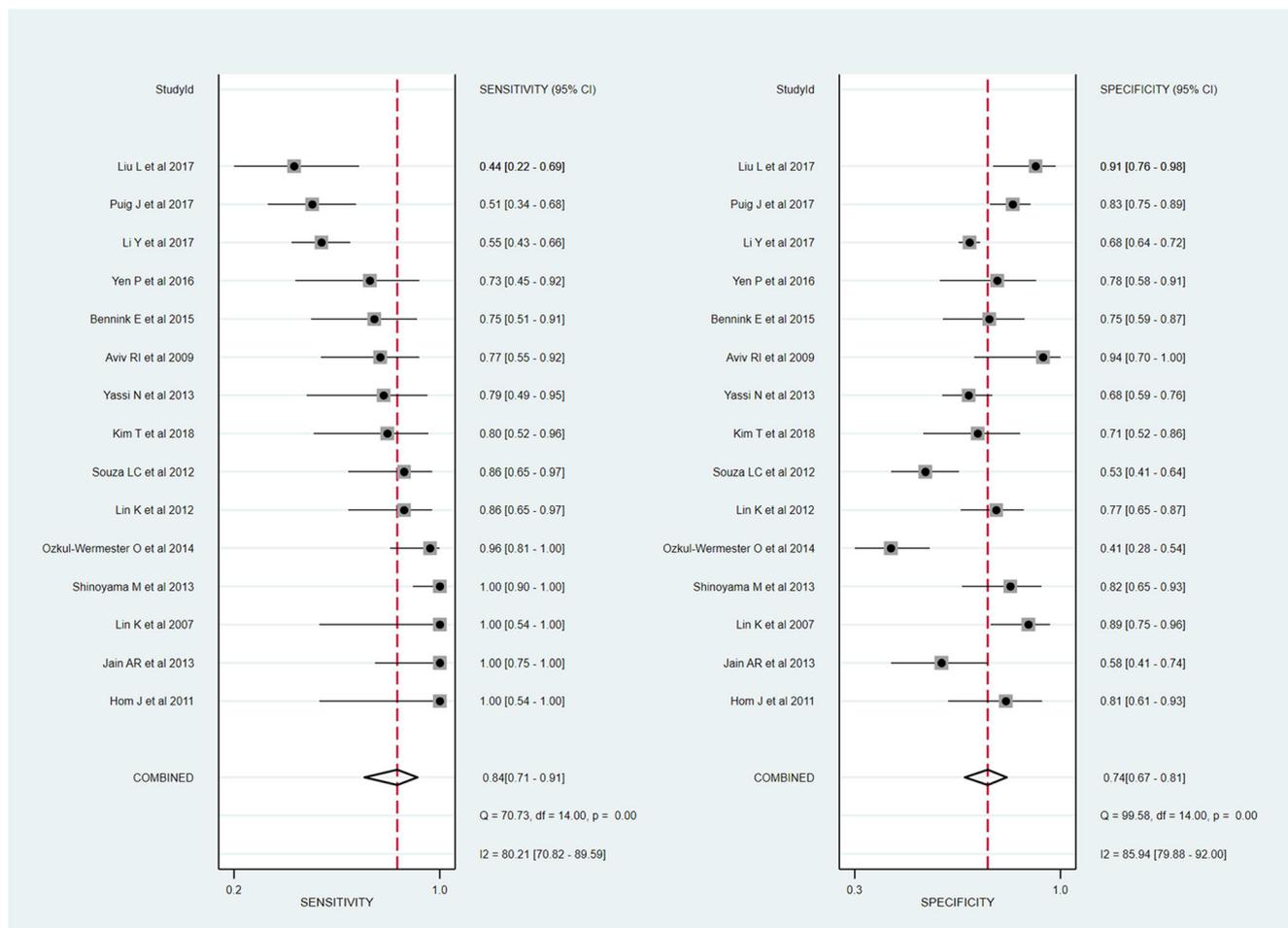


Fig. 2 Coupled forest plots of the pooled sensitivity and specificity for the diagnostic performance of perfusion CT for prediction of hemorrhagic transformation in acute ischemic stroke. Numbers are pooled estimates

with 95% confidence intervals (CIs) in parentheses; horizontal lines indicate 95% CIs

supports the use of perfusion CT for predicting hemorrhagic transformation in acute ischemic stroke.

The 2018 American Heart Association/American Stroke Association (AHA/ASA) guideline recommends non-contrast CT for initial brain imaging evaluation and CT angiography for vessel evaluation if patients are suspected of having intracranial large vessel occlusion [43]. In addition, perfusion CT is recommended within 6 to 24 h of symptom onset for selected acute ischemic stroke patients with large vessel occlusion in the anterior circulation [43]. Multimodal CT protocols are rapidly accessible and widely available and are already part of the routine protocol in many stroke centers. Perfusion CT can be a part of these multimodal CT protocols and can provide multiple parameters in a fast and easy acquisition. The one drawback of perfusion CT is the radiation dose; however, the present study revealed reasonable reported radiation doses ranging from 2.7 to 7.9 mSv. There are several clinical applications for perfusion CT in acute ischemic stroke. First, perfusion CT can be used to predict the final infarct core or the extent of the penumbra [44, 45]. Second, perfusion CT

can also be used to predict clinical outcomes in stroke patients treated with thrombectomy [46, 47]. Third, as the present study highlights, perfusion CT can be used to predict hemorrhagic transformation in acute ischemic stroke. This study demonstrates that perfusion CT has a moderate pooled sensitivity of 84% (95% CI, 71–91%) and specificity of 74% (95% CI, 67–81%) for the prediction of hemorrhagic transformation in acute ischemic stroke.

Recently, blood-brain barrier permeability imaging, which models the extravasation of contrast agent from the intravascular space to the extravascular space, has been introduced for the prediction of hemorrhagic transformation in acute ischemic stroke [8–10, 12–14, 17, 18, 22]. Microvascular permeability expressed as PS is a metric representing blood-brain barrier permeability [14]. PS indicates the rate of contrast agent extravasation from the intravascular space to the extravascular space through a disrupted blood-brain barrier [48]. K^{trans} also represents the product of endothelial permeability and endothelial surface area [13]. In the present study, 60% of included studies used permeability-related parameters (i.e., PS

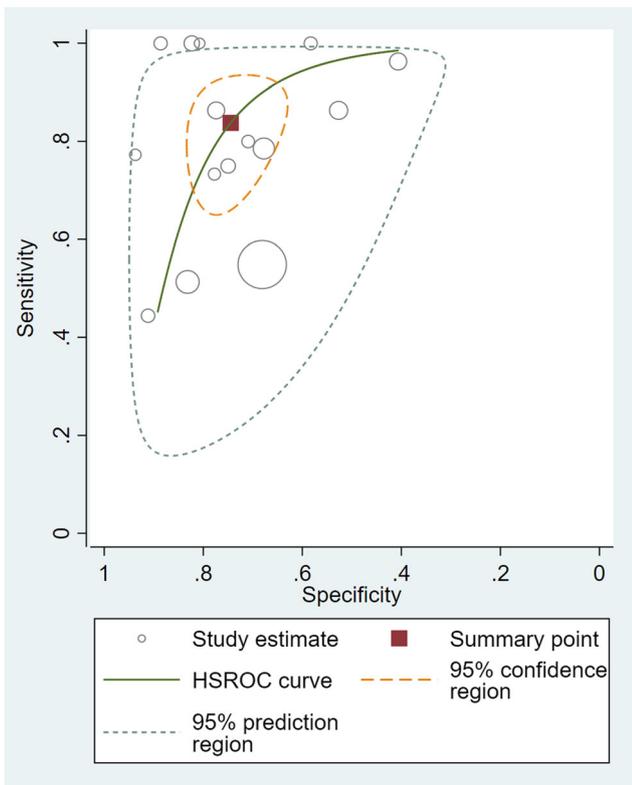


Fig. 3 Hierarchical summary receiver operating characteristic (HSROC) curve of the diagnostic performance of perfusion CT for prediction of hemorrhagic transformation in acute ischemic stroke

and K^{trans}) to predict hemorrhagic transformation [8–10, 12–14, 17, 18, 22], and we found that increased PS [8, 9, 14, 17, 22] or K^{trans} [10, 12, 13] predisposes patients to hemorrhagic transformation after reperfusion therapy.

Hypoperfusion status is also known to be associated with hemorrhagic transformation [11, 15, 20, 21]. We showed lower CBV [11, 15], lower CBF [20], and prolonged Tmax values [21] in the hemorrhagic transformation group in comparison with the non-hemorrhagic transformation group. These results appear to be in agreement with the hypothesis that hemorrhagic transformation is a consequence of severe ischemic damage to vessel walls, which then proceeds to blood-brain barrier disruption and leakage [49].

We found that the sensitivity ($I^2 = 80.21\%$) and specificity ($I^2 = 85.94\%$) were subject to study heterogeneity. To overcome this study heterogeneity, we additionally performed multiple subgroup analyses. Although our subgroup analyses may have explained some of the study heterogeneity, a part remains unexplained. It has been postulated that main reasons for heterogeneity across CT perfusion studies are different CT scanners used in different studies, discrepancies in CT perfusion methodology, and different perfusion metrics quantified. If perfusion CT is to be used as a routine stroke protocol, the

standardization of perfusion CT techniques and the determination of optimal parameter cutoff values for predicting hemorrhagic transformation are critical.

We note the following limitations to this study. First, various follow-up intervals and imaging modalities were used to determine the reference standard. Second, there were differences in cutoff values for perfusion CT parameters across the included studies. Third, there was a publication bias among the included studies ($p = 0.01$). We believe that this publication bias may have been present because studies with more significant results are more likely to be published. Therefore, there is the possibility that the diagnostic performance of perfusion CT for prediction of hemorrhagic transformation in acute ischemic stroke might have been overestimated. To overcome these limitations, we used robust methodology such as hierarchical logistic regression modeling [25–27] and reported our manuscript in accordance with the following guidelines: PRISMA [23], Handbook for Diagnostic Test Accuracy Reviews (Cochrane Collaboration) [50], and the Agency for Healthcare Research and Quality (AHRQ) [51]. Third, hemorrhagic transformation in acute ischemic stroke is a multifactorial process and cannot be reviewed only from the side of perfusion changes. Other factors including lesion size, location, duration of vessel occlusion, and preceding microbleeds might predict the hemorrhagic transformation of acute ischemic stroke [8, 15, 17, 18]. Therefore, the use of CT perfusion, which is vulnerable to additional ionizing radiation, should be considered with caution when applying our results to daily clinical practice and should be compared to the predictive value of other data.

In conclusion, high blood-brain barrier permeability and hypoperfusion status derived from perfusion CT are associated with hemorrhagic transformation. Although various perfusion CT parameters were used across the different studies, the current evidence supports the use of perfusion CT for predicting hemorrhagic transformation in acute ischemic stroke.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Seung Chai Jung.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors (Chong Hyun Suh) has significant statistical expertise (5 years of experience in a systematic review and meta-analysis).

Informed consent Written informed consent was not required for this study because of the nature of our study, which was a systemic review and meta-analysis.

Ethical approval Institutional Review Board approval was not required because of the nature of our study, which was a systemic review and meta-analysis.

Methodology

- a systemic review and meta-analysis
- performed at one institution

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