

# Diagnostic Accuracy of CT Perfusion Imaging for Detecting Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

J.M. Biesbroek<sup>b</sup> J.M. Niesten<sup>a</sup> J.W. Dankbaar<sup>a</sup> G.J. Biessels<sup>b</sup> B.K. Velthuis<sup>a</sup>  
J.B. Reitsma<sup>c</sup> I.C. van der Schaaf<sup>a</sup>

Departments of <sup>a</sup>Radiology, and <sup>b</sup>Neurology, Rudolf Magnus Institute of Neuroscience, and <sup>c</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

## Key Words

CT perfusion · Ischemic stroke · Sensitivity · Specificity · Acute stroke

## Abstract

**Background:** The aim of the current study was to determine the sensitivity and specificity of CT perfusion (CTP) for the detection of ischemic stroke by performing a systematic review and meta-analysis of published reports. **Methods:** We searched PubMed, Embase and the Cochrane library using the terms ‘perfusion computed tomography’, ‘ischemic stroke’ and synonyms. We included studies that: (1) reported original data, (2) studied the diagnostic value of CTP for detecting ischemic stroke, (3) used MRI-DWI, follow-up MRI or follow-up CT as the reference standard, (4) included at least 10 patients who were suspected of ischemic stroke, and (5) reported the number of true positives, true negatives, false positives and false negatives for the diagnosis of ischemic stroke. **Results:** Fifteen studies were finally included in the current review with a total of 1,107 patients. A pooled analysis resulted in a sensitivity of 80% (95% confidence interval, CI: 72–86%) and a specificity of 95% (95% CI: 86–98%). Almost two thirds of the false negatives were due to small lacunar infarcts; the remaining false negatives were mostly

due to limited coverage. **Conclusions:** The current systematic review shows that CTP has a high sensitivity and a very high specificity for detecting infarcts.

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## Introduction

On arrival to the emergency department, patients with symptoms of acute ischemic stroke are often evaluated with CT perfusion (CTP). Adding CTP to non-contrast CT has been shown to increase the diagnostic accuracy for the detection of ischemia [1]. Furthermore, CTP can be used to determine the extent and potential reversibility of ischemia. This may be helpful in selecting patients who are likely to benefit from thrombolytic therapy [2–6].

Although promising, CTP does not always accurately predict the presence or absence of ischemic stroke. An ischemic lesion may not be detected, leading to a false-negative evaluation of the CTP images. In addition, several diseases such as extracranial carotid artery stenosis and proximal intracranial stenosis can mimic perfusion

J.M.B. and J.M.N. contributed equally to this paper.

patterns seen in acute cerebral ischemia, leading to a false-positive evaluation [7–10].

Since its introduction, the accuracy of CTP for detecting ischemic stroke has been the subject of several studies. To date, a systematic review comparing these studies has not been performed. The purpose of our study is to systematically review published reports to determine the sensitivity and specificity of CTP for the detection of ischemic stroke.

## Methods

### *Search Strategy*

We searched PubMed, Embase and the Cochrane library using the terms ‘perfusion computed tomography’, ‘ischemic stroke’ and synonyms (the complete search syntax is provided in online suppl. table 1; for all online suppl. material, see [www.karger.com/doi/10.1159/000350200](http://www.karger.com/doi/10.1159/000350200)). All papers published until May 5, 2012, were included. Titles and abstracts of the obtained articles were screened for relevance. The full text of articles that were eligible for inclusion based on the title and abstract were read and assessed for inclusion independently by 2 authors (J.M.B. and J.M.N.). Disagreements were resolved by consensus. The bibliographies of the included articles were screened to find additional eligible reports.

### *Inclusion and Exclusion Criteria*

We included studies that: (1) reported original data, (2) studied the diagnostic value of CTP for detecting ischemic stroke, (3) used MRI-DWI, follow-up MRI or follow-up CT as the reference standard, (4) included at least 10 patients who were suspected of ischemic stroke, and (5) reported the number of true positives, true negatives, false positives and false negatives for the diagnosis of ischemic stroke. All study designs (prospective and retrospective) were included. Studies that used duplicate data were excluded. If a study supplied insufficient data to meet the inclusion criteria, an effort was made to contact the study authors to request additional information; if there was no response, the study was excluded.

### *Data Extraction*

Data were extracted from all included articles by two authors (J.M.B. and J.M.N.). Disagreements were resolved by consensus. Extracted data included study population characteristics, technical information regarding the CTP acquisition, the proportion of patients with ischemic stroke as determined by the reference standard and the accuracy of CTP (number of true and false positives and true and false negatives) for the diagnosis of ischemic stroke. The methodological quality of each study was assessed using the QUADAS criteria, with a maximum score of 13 points (online suppl. table 2) [11]. Specific guidance for scoring the items was developed acknowledging the specific characteristics of the current review.

### *Statistical and Data Analysis*

We used a bivariate, random effects model to meta-analyze the pairs of sensitivity and specificity calculated from each study in order to obtain summary estimates with corresponding 95%

confidence intervals (CI). The bivariate approach simultaneously models the logit-transformed sensitivity and specificity from studies, thereby incorporating any correlation that might exist between these measures. The model uses a random effects approach for both sensitivity and specificity, allowing for heterogeneity beyond chance due to clinical and methodological differences between studies. Forest plots of sensitivity and specificity with their corresponding 95% CI using the Wilson method were generated.

Covariates were added to the bivariate model to examine whether sensitivity and/or specificity were different depending on specific study characteristics. These subgroup analyses were performed on: (1) only studies with a prospective design (8 studies), (2) only studies in which patients were scanned within 6 h of the onset of symptoms (8 studies), and (3) including only patients in which the false-negative findings were not due to limited brain coverage (536 patients).

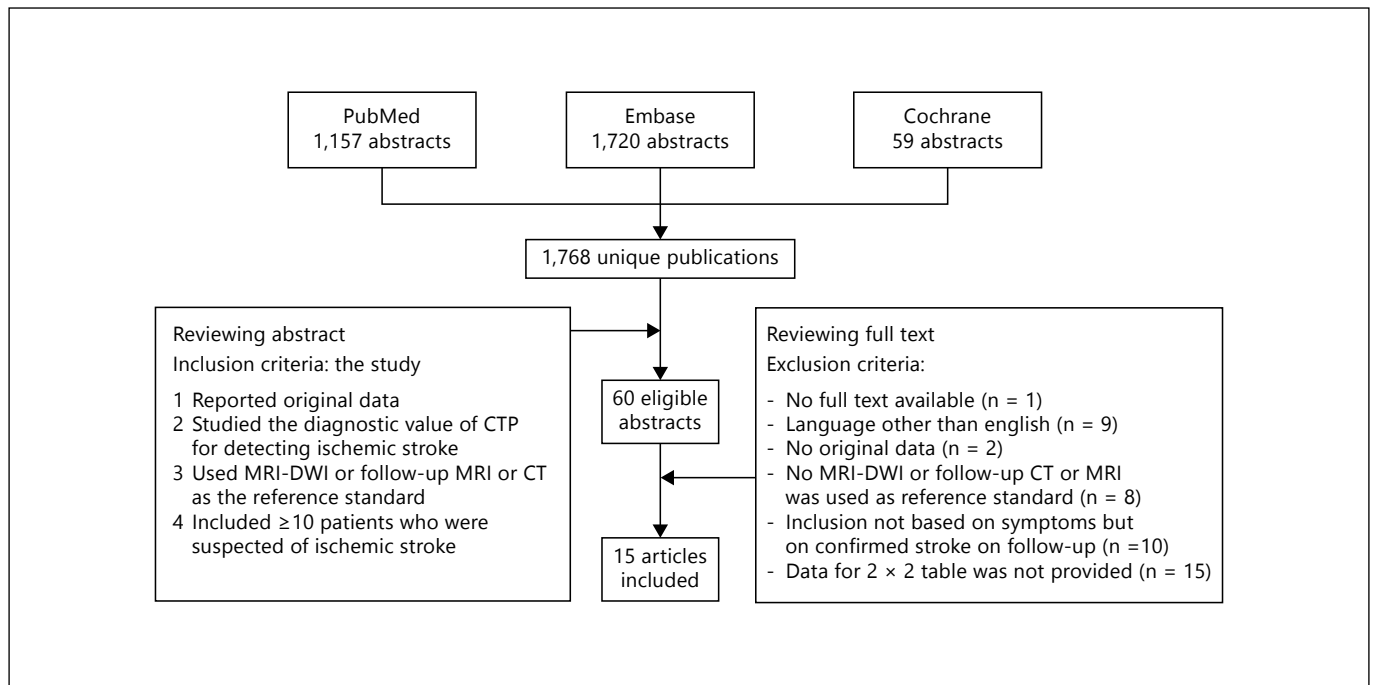
The non-linear mixed models procedure (PROC NLMIXED) of SAS (version 9.2, SAS Institute, Cary, N.C., USA) was used to estimate the parameters of the bivariate models. Other analyses were performed with StatXact (version 6.0, Cytel Software Corporation, Cambridge, Mass., USA). In the subgroup analyses, *p* values below 0.05 were considered statistically significant.

## Results

Our search yielded 1,768 unique results. After screening title and abstract, 60 papers were selected for full text screening. The bibliographies of the included articles did not result in the inclusion of additional studies, thereby validating the applied search string. After screening the full text of these 60 articles, 15 articles [1, 12–25] were finally included in the current study. A flow chart of the inclusion of studies is provided in figure 1.

### *Study Characteristics*

Patient characteristics, the proportion of patients with a final diagnosis of stroke, and the QUADAS score of the included studies are summarized in table 1. The 15 included studies totaled 1,107 patients with a median of 42 patients per study (range 12–422). Eight studies had a prospective design and 5 studies a retrospective design (not specified in 2 studies). None of the studies excluded patients with a lacunar syndrome. The maximum time between the onset of clinical symptoms and CTP acquisition ranged from 3 to 24 h; mean time from symptom onset (provided by 9 out of 15 studies) ranged from 2.3 to 5.5 h. Two studies excluded patients who received thrombolytic therapy; for the remaining studies, the proportion of treated patients ranged from 17 to 59% (not specified in 4 studies). The proportion of patients with a final diagnosis of ischemic stroke ranged from 37



**Fig. 1.** Flowchart of search strategy and selection of reports. The search was conducted on May 5, 2012.

**Table 1.** Characteristics of included studies

Study	Year	Study design	Patients	NIHSS mean (SD)	Time to CTP, h <sup>1</sup>	Patients thrombolysed	Reference standard	Time to reference standard <sup>2</sup>	Stroke	QUADAS score
Eckert	2010	P	107	8.3 (NS)	6 (NS)	51 (48%)	FU MR or CT	2–5 days	76 (71%)	11
Lin	2009	R	100	12 (4–28) <sup>3</sup>	3 (NS)	25 (25%)	DWI	<7 days	65 (65%)	11
Rai	2008	R	422	NS	15 (3.9)	0 <sup>4</sup>	DWI	<7 days	157 (37%)	12
Youn	2008	R	58	NS	24 (3.4)	14 (24%)	DWI	<27 h	51 (88%)	12
Langer	2007	P	50	6 (0–28) <sup>3</sup>	8 (NS)	NS	FU CT	>48 h	38 (76%)	8
Suzuki	2005	NS	118	NS	10 (NS)	20 (17%)	FU MR or CT	NS	110 (93%)	5
Wintermark	2005	R	46	NS	12 (5.5)	0 <sup>4</sup>	FU MR or CT	2–18 days	26 (57%)	13
Esteban	2004	R	42	NS	6 (NS)	NS	FU MR or CT	1–2 days	29 (69%)	10
Kloska	2004	P	41	10.5 (NS) <sup>5</sup>	8 (3.1)	NS	FU MR or CT	1–11 days	38 (93%)	11
Schramm	2004	P	22	10 (4–28) <sup>3</sup>	6 (2.3)	13 (59%)	FU CT	5 days	13 (59%)	11
Eastwood	2003	P	15	12.6 (5.9)	8 (3.1)	3 (20%)	DWI	<11 h	14 (93%)	11
Roberts	2001	NS	12	NS	6 (NS)	NS	FU MR or CT	>1 day	9 (75%)	7
Rother	2000	P	22	13.2 (5.2)	6 (2.4)	6 (27%)	FU CT	NS	20 (91%)	9
Reichenbach	1999	P	20	NS	6 (2.8)	7 (35%)	FU MR or CT	NS	20 (100%)	7
Koenig	1998	P	32	NS	6 (2.7)	10 (31%)	FU MR or CT	NS	28 (88%)	7

R = Retrospective; P = prospective; NS = not stated.

<sup>1</sup> Time from the onset of symptoms to CTP acquisition expressed as maximum (mean).

<sup>2</sup> Time from the onset of symptoms to reference standard acquisition.

<sup>3</sup> Median with range provided instead of mean.

<sup>4</sup> Patients who were treated with thrombolysis were excluded.

<sup>5</sup> Mean NIHSS provided for 44 patients, 3 of whom were excluded from the analysis because they suffered infratentorial stroke.

**Table 2.** Perfusion CT acquisition and review methods of the included studies

Study	CT scanner used	Brain coverage mm	Slice thickness mm	Temporal resolution ms	Software used	Color maps used	Review method
Eckert	Philips 40 slice	40	10	1,500	deconvolution	CBV, MTT	visual assessment
Lin	Siemens 16 slice	24	12	1,000	maximum slope	TTP, CBV, CBF	visual assessment
Rai	GE multislice <sup>1</sup>	20	10	500	deconvolution	CBV, CBF, MTT	visual assessment
Youn	Philips 64 slice	80	10	4,000	deconvolution	TTP, CBV, CBF, MTT	visual assessment
Langer	GE multislice <sup>1</sup>	NS	NS	800	deconvolution	CBV, CBF, MTT	visual assessment
Suzuki	GE 64 slice	30	10	2,000	deconvolution	CBV, CBF, MTT	visual assessment
Wintermark	Philips multislice <sup>1</sup>	40	10	1,000	deconvolution	TTP, CBV, CBF, MTT	visual assessment
Esteban	GE 16 slice	20	5–10	1,000	deconvolution	CBV, CBF, MTT	visual assessment
Kloska	Siemens 4 slice	20	10	1,000	maximum slope	TTP, CBV, CBF	visual assessment
Schramm	Siemens multislice <sup>1</sup>	20	10	1,000	maximum slope	TTP, CBV, CBF	visual assessment
Eastwood	GE 1 slice	5–10	5–10	500–1,000	deconvolution	CBV, CBF, MTT	threshold <sup>2</sup>
Roberts	GE multislice <sup>1</sup>	40	10	5,000	deconvolution	TTP, CBV, CBF, MTT	visual assessment
Rother	Siemens slip-ring	10	10	1,000–1,600	deconvolution	TTP	threshold <sup>3</sup>
Reichenbach	Siemens slip-ring	10	10	1,000	deconvolution	TTP	visual assessment
Koenig	Siemens slip-ring	10	10	1,000	maximum slope	CBF	visual assessment

TTP = Time to peak; CBV = cerebral blood volume; CBF = cerebral blood flow; MTT = mean transit time.

<sup>1</sup> Only information about CT vendor provided.

<sup>2</sup> Defined thresholds: CBV <1.5 ml/100 g; CBF <10 ml/100 g/min; MTT >6 s.

<sup>3</sup> Defined threshold: TTP >6 s delay.

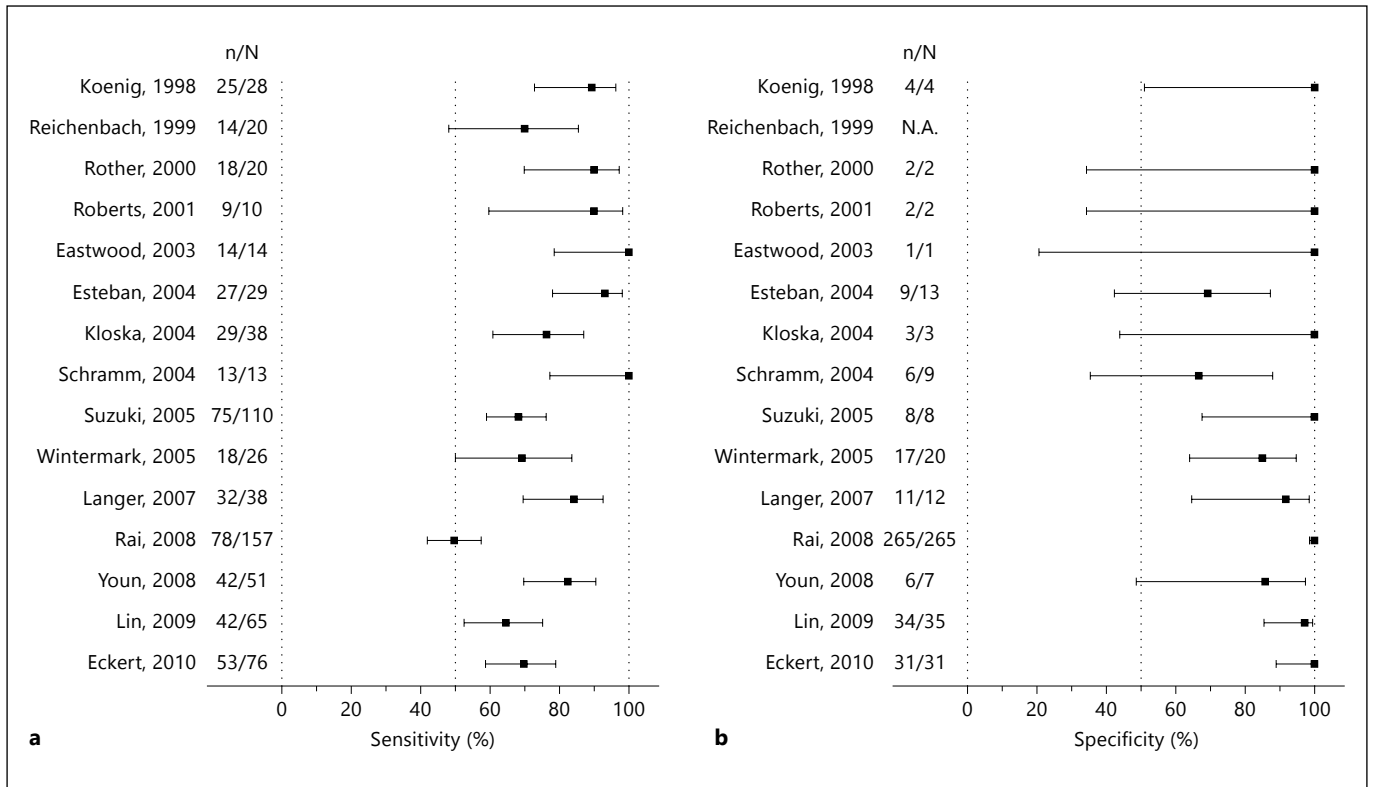
to 100% (median 76%). The quality of the included studies as assessed by the QUADAS tool varied considerably (median QUADAS score 11; range 5–13).

Data regarding the acquisition, postprocessing and review methods of CTP are summarized in table 2. Brain coverage ranged from 5–10 to 80 mm (median 20 mm) and the slice thickness was either 5 or 10 mm in all studies (not specified in 1 study). Temporal resolution varied from 500 to 5,000 ms (median 1,000 ms). Four studies used postprocessing software that was based on the maximum slope model compared to 11 studies that used de-

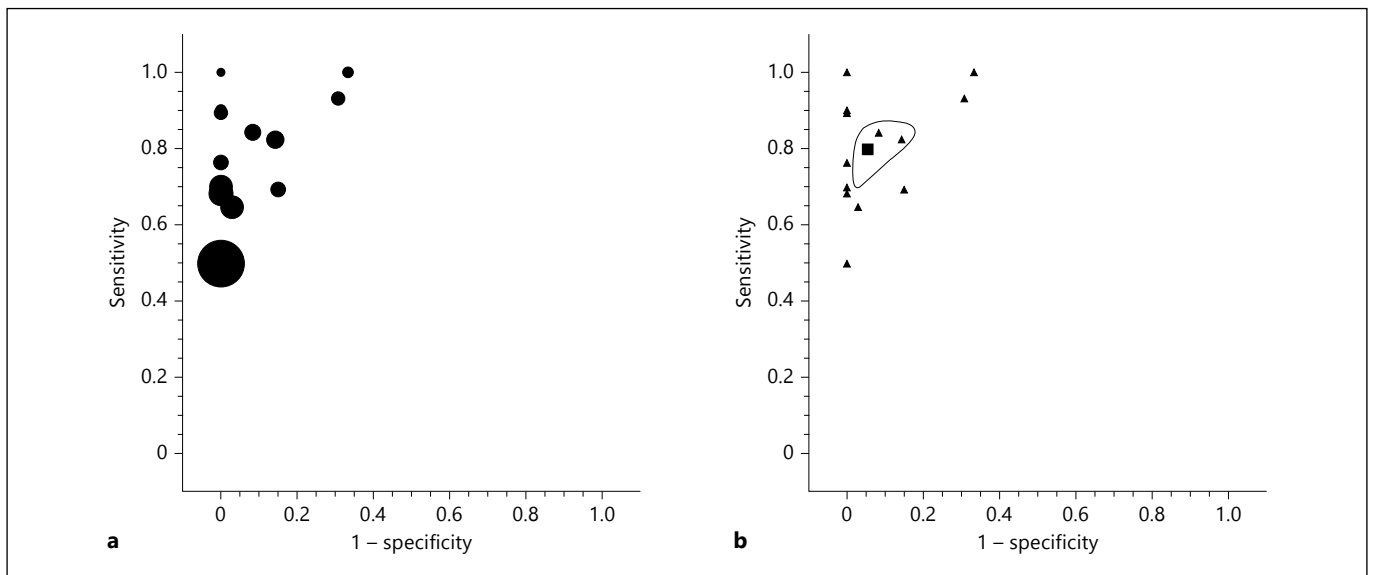
convolution-based software. The CTP color maps were reviewed by ‘visual assessment’ in 13 studies; 2 studies used thresholds for defining infarcted tissue.

#### *Diagnostic Accuracy*

The sensitivity and specificity of CTP for diagnosing ischemic stroke as reported by the 15 included studies are shown in figure 2. A pooled analysis resulted in a sensitivity of 80% (95% CI: 72–86%) and a specificity of 95% (95% CI: 86–98%). The pooled sensitivity and specificity are presented in figure 3.



**Fig. 2. a** Sensitivity of CTP for detecting ischemic stroke. n = Number of true positives; N = number of true positives + number of false negatives. **b** Specificity of CTP for detecting ischemic stroke. n = Number of true negatives; N = number of true negatives + number of false positives.



**Fig. 3. a** Diagnostic accuracy of the included studies for detecting ischemic stroke. The circle size represents the sample size of the corresponding study. **b** 95% confidence ellipse around mean sensitivity and specificity, which is represented by the square. The triangles represent the sensitivity and specificity of each included study.

**Table 3.** Pooled analyses

	Studies	Patients	Sensitivity, % (95% CI)	Specificity, % (95% CI)
All studies	15	1,107	80 (72–86)	95 (86–98)
Prospective study design	8	309	85 (75–92)	97 (77–100)
<6 h between symptom onset and CTP acquisition	8	357	83 (73–90)	94 (76–99)
After exclusion FN due to limited coverage	13	536	89 (81–94)	90 (79–96)

FN = False negatives.

### *False Negatives and False Positives*

Thirteen studies specified the false-negative findings. In these 92 false-negative CTP findings, the missed infarcts were located outside the CTP-covered brain area in 31 patients (online suppl. table 3). In 61 patients, the missed infarct was located within the covered brain area; five of these were missed due to motion artifacts; 54 patients had a lacunar infarct and 2 had a territorial infarct. Rai et al. [13] and Suzuki et al. [16] did not specify the location and type of infarct for all false-negative findings. In all 15 studies combined, false-positive findings (i.e. perfusion deficits without an ischemic lesion on follow-up imaging) were reported in 13 patients. Seven of these patients were diagnosed with transient ischemic attack which might have resulted in a transient perfusion deficit; in 1 patient, the false-positive finding was due to a chronic ischemic lesion; the cause was not specified in 5 patients.

### *Subgroup Analyses*

The results of the subgroup analyses are summarized in table 3. In the first subgroup analysis, including only studies (n = 8) with a prospective design, the sensitivity increased to 85% (95% CI: 75–92%) and specificity increased slightly to 97% (95% CI: 77–100%). There were no statistically significant differences in sensitivity (p = 0.11) and specificity (p = 0.73) between prospective and retrospective studies. In the second subgroup analysis, including only studies (n = 8) that stated that all patients underwent CTP within 6 h of symptom onset, sensitivity increased slightly to 83% (95% CI: 73–90) and specificity decreased slightly to 94% (95% CI: 76–99). The increase in sensitivity (p = 0.29) and decrease in specificity (p = 0.73) were not statistically significant. In the third subgroup analysis, including only the 13 studies that specified the false-negative findings and excluding 31 false-negative findings due to limited brain coverage, sensitivity increased to 89% (95% CI: 81–94%) and specificity decreased to 90% (95% CI: 78–96).

### **Discussion**

The findings of the current systematic review show that CTP has a very high specificity and a high sensitivity for the diagnosis of ischemic stroke. False negatives mainly occurred in cases of small lacunar infarcts. Other causes for false negatives were limited brain coverage and motion artifacts.

The sensitivity of CTP varied considerably between studies, which is probably due to the heterogeneity in patient characteristics, CTP spatial and temporal resolution and postprocessing methods. Therefore, the point estimates for sensitivity and specificity from our meta-analysis should be interpreted with some caution. We identified several potential sources of heterogeneity. Firstly, the proportion of patients with lacunar infarcts varied between studies. Patients with lacunar infarcts should not be excluded when studying the diagnostic accuracy of CTP because in the acute phase lacunar syndromes cannot always be distinguished clinically from non-lacunar infarcts, and both groups are likely to benefit from thrombolytic therapy [26]. Secondly, the maximum time between symptom onset and CTP scan acquisition varied between studies. Larger time interval between symptom onset and CTP acquisition might be expected to increase sensitivity because after 6–12 h ischemia can also be visible on unenhanced CT. To assess this, a subgroup analysis was performed including only studies that stated that all patients underwent CTP within 6 h of the onset of symptoms. This time window was chosen because intra-arterial thrombolysis in patients with anterior circulation ischemic stroke is recommended and generally performed within 6 h [27–29]. In this analysis, sensitivity and specificity remained essentially the same. Thirdly, the proportion of patients with a confirmed diagnosis of ischemic stroke ranged from 37 to 100%, which may reflect differences in patient selection. Fourthly, coverage and tempo-

ral resolution of CTP imaging varied between studies. The oldest studies used only one CTP slice 5–10 mm in width, whereas more recent studies used CTP with up to 8 slices 10 mm in width. In the past few years, CT scanners that allow CTP imaging of the entire brain with good temporal resolution have been introduced and are likely to improve the sensitivity of CTP. In the subgroup analysis in which 31 false-negative findings due to limited brain coverage were excluded, sensitivity increased from 80 to 89%. However, many institutions still use CT scanners without full brain coverage. Youn et al. [14] and Roberts et al. [22] used the ‘toggling table’ technique which results in a doubled volume coverage at the cost of decreased temporal resolution which may decrease spatial resolution if the arterial curves are undersampled. Fifthly, postprocessing of the raw CTP data differed between studies. Eleven studies used deconvolution-based software to calculate the CTP color maps, whereas 4 studies used maximum slope-based software. However, these two different types of software have been shown to yield comparable qualitative and quantitative results [30]. None of the studies used tracer delay-insensitive perfusion algorithms in their software. It has recently been shown that using tracer delay-sensitive methods will result in an overestimation of the perfusion abnormalities in stroke patients [31]. This may have contributed to false-positive evaluation of CTP maps. However, this occurred only in a total of 13 patients in the studies analyzed in this review. Another potential cause of false-positive findings is transient ischemia that might have resulted in a perfusion deficit that did not correspond with an ischemic lesion on follow-up. Sixthly, 8 studies had a prospective design, 5 studies had a retrospective design and 2 studies did not specify their design. We performed a subgroup analysis including only the 8 prospective studies which showed a slight, but statistically insignificant increase in sensitivity (80–85%) and specificity (95–97%). Therefore, the impact of differences in study design of the included studies on diagnostic accuracy appears to be small. Finally, the CTP color map review methods varied between studies. In 13 studies, the CTP color maps were subjectively reviewed by ‘visual assessment’, whereas 2 studies applied thresholds. Currently, no consensus exists regarding optimal thresholds to distinguish infarct core and penumbra from well-perfused brain tissue [32]. The 2 studies using thresholds showed similar sensitivity and specificity compared to the other 13 studies. Currently, most postprocessing software packages provide a summary map in addition to the color maps. This summary map estimates the size and location of the infarct core and penumbra and enables quick inter-

pretation by neurologists and radiologists in both academic and non-academic centers. The summary map results from software-dependent thresholds of quantitative perfusion values. Frequently used thresholds to calculate summary maps are a prolonged MTT of more than 145% compared to the non-ischemic hemisphere to identify the whole ischemic region in combination with absolute CBV values to differentiate infarct core (CBV <2.0 ml/100 g) from potentially salvageable penumbra (CBV ≥2.0 ml/100 g) [33]. However, some software packages apply other thresholds or use other perfusion parameters (for example CBF) to estimate the infarct core and penumbra. Using different thresholds or perfusion parameters to estimate penumbra and infarct core can result in large differences in summary maps [34]. These findings emphasize the need for standardization of CTP analysis algorithms and software.

Since CTP has improved in the last decade, the reported diagnostic accuracy might be an underestimation of the accuracy that may be achieved using contemporary software and full brain coverage. New postprocessing techniques have been developed to improve the detection of lacunar infarcts [35], and full coverage has been shown to improve the detection of ischemic lesions [36]. Since the current review, based on relatively older studies, shows that CTP has a high sensitivity and very high specificity for detecting ischemic stroke, diagnostic accuracy will only increase with newer software and full brain coverage.

The use of CTP has some considerations that need to be addressed. Firstly, acute CT stroke protocols (with CTP and CTA arch to vertex) require more time than noncontrast CT alone, although only in the order of minutes [35, 37]. Secondly, due to iodinated contrast administration, around 2–3% of patients develop a contrast-induced nephropathy; however, the risk for developing long-term renal sequelae is negligible [36–39]. Thirdly, CTA and CTP increase the radiation dose with around 4–6 times on average compared to the dose of an unenhanced CT scan of the head, depending on the scan parameters used [38–41]. The results of our review suggest that increased brain coverage might increase the accuracy of CTP. However, a 14 cm full brain coverage scan with a 320-detector row CT increases the effective radiation doses by around 40% when compared to 3.2 cm coverage with a 64-row CT [40, 42]. Several new technical modifications and recently introduced reduction techniques like iterative reconstruction can help to reduce radiation exposure [41, 43]. Therefore, a combination of newer scanners with new technical modifications and reduction techniques might lead to improved diagnostic accuracy at

an acceptable radiation dose. CTP has been shown to be at least two times more sensitive than noncontrast CT alone for detecting acute ischemic stroke and can facilitate the clinical treatment decision-making [1, 5]. Diffusion-weighted MRI is considered the most accurate imaging modality for detecting acute ischemic stroke, with a very high sensitivity (88–100%) and specificity (95–100%) [27]. Furthermore, in multimodal MR including perfusion-weighted imaging, the penumbra can be estimated as regions of perfusion change without a corresponding diffusion abnormality (diffusion-perfusion mismatch) [27]. Advantages of the multimodal CT approach over MRI include wider availability of emergency CT imaging, rapid imaging, and fewer contraindications to CT versus MRI [27]. Current treatment protocols for the emergency management (i.e. thrombolysis and thrombectomy) of patients with acute ischemic stroke are not yet based on perfusion imaging [27]. A number of studies have pro-

vided support for perfusion imaging-based selection for the treatment of acute ischemic stroke [44–47]. However, there is currently insufficient evidence that perfusion imaging-based treatment protocols result in improved clinical outcome [48].

The current systematic review shows that CTP has a high sensitivity and a very high specificity for detecting infarcts. Spatial resolution remains an important limitation of CTP since almost two thirds of the false negatives were due to small lacunar infarcts. Another drawback in CTP until recently has been the limited brain coverage. However, recently introduced CT systems that are equipped with new postprocessing techniques and allow full brain CTP could resolve these issues, and will likely further improve the diagnostic accuracy of CTP. Therefore, future studies should focus on increasing sensitivity for the detection of lacunar infarcts by optimizing CTP techniques.

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