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CTP for the Screening of Vasospasm and Delayed Cerebral Ischemia in Aneurysmal SAH: A Systematic Review and Meta-analysis

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ABSTRACT

BACKGROUND: Delayed cerebral ischemia and vasospasm are the most common causes of late morbidity following aneurysmal SAH, but their diagnosis remains challenging.

PURPOSE: This systematic review and meta-analysis investigated the diagnostic performance of CTP for detection of delayed cerebral ischemia and vasospasm in the setting of aneurysmal SAH.

DATA SOURCES: Studies evaluating the diagnostic performance of CTP in the setting of aneurysmal SAH were searched on the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Clinical Answers, Cochrane Methodology Register, Ovid MEDLINE, EMBASE, American College of Physicians Journal Club, Database of Abstracts of Reviews of Effects, Health Technology Assessment, National Health Service Economic Evaluation Database, PubMed, and Google Scholar from their inception to September 2023.

STUDY SELECTION: Thirty studies were included, encompassing 1786 patients with aneurysmal SAH and 2302 CTP studies. Studies were included if they compared the diagnostic accuracy of CTP with a reference standard (clinical or radiologic delayed cerebral ischemia, angiographic spasm) for the detection of delayed cerebral ischemia or vasospasm in patients with aneurysmal SAH. The primary outcome was accuracy for the detection of delayed cerebral ischemia or vasospasm.

DATA ANALYSIS: Bivariate random effects models were used to pool outcomes for sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio. Subgroup analyses for individual CTP parameters and early-versus-late study timing were performed. Bias and applicability were assessed using the modified QUADAS-2 tool.

DATA SYNTHESIS: For assessment of delayed cerebral ischemia, CTP demonstrated a pooled sensitivity of 82.1% (95% CI, 74.5%–87.8%), specificity of 79.6% (95% CI, 73.0%–84.9%), positive likelihood ratio of 4.01 (95% CI, 2.94–5.47), and negative likelihood ratio of 0.23 (95% CI, 0.12–0.33). For assessment of vasospasm, CTP showed a pooled sensitivity of 85.6% (95% CI, 74.2%–92.5%), specificity of 87.9% (95% CI, 79.2%–93.3%), positive likelihood ratio of 7.10 (95% CI, 3.87–13.04), and negative likelihood ratio of 0.16 (95% CI, 0.09–0.31).

LIMITATIONS: QUADAS-2 assessment identified 12 articles with low risk, 11 with moderate risk, and 7 with a high risk of bias.

CONCLUSIONS: For delayed cerebral ischemia, CTP had a sensitivity of >80%, specificity of >75%, and a low negative likelihood ratio of 0.23. CTP had better performance for the detection of vasospasm, with sensitivity and specificity of >85% and a low negative likelihood ratio of 0.16. Although the accuracy offers the potential for CTP to be used in limited clinical contexts, standardization of CTP techniques and high-quality randomized trials evaluating its impact are required.

ABBREVIATIONS: aSAH = aneurysmal SAH; DCI = delayed cerebral ischemia; LR = likelihood ratio; rCBF = relative CBF; rCBV = relative CBV; Tmax = time-to-maximum

SAH from ruptured intracranial aneurysms (aneurysmal SAHs [aSAHs]) accounts for 5% of all strokes, with 1 in 5 survivors experiencing disability or cognitive impairment.[1,2] In the era of early endovascular and surgical treatment of aneurysms, delayed cerebral ischemia (DCI) is the most common cause of late morbidity in these patients.[2]

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DCI is clinically defined as the development of focal neurologic impairment (including hemiparesis, aphasia, or neglect) or decreased consciousness of at least 2 points on the Glasgow Coma Scale. This should last >1 hour, is not apparent immediately after aneurysm occlusion, and is not attributable to other causes by means of clinical assessment, CT, or MR imaging investigation of the brain and appropriate laboratory studies.[3] Cerebral infarction resulting from DCI is defined as the appearance of established hypodensity on CT or territorial ischemia on MR imaging within 6 weeks of SAH.[3] It may commence as early as day 3 after aneurysm rupture, with the peak incidence at days 7–10.[3,4] The diagnosis of DCI is challenging due to confounding factors, including impaired CSF transport, sedation, cerebral edema, coexistent cerebrovascular disease, or vascular stenosis due to treatment devices. Early recognition of DCI allows endovascular treatment before it leads to cortical infarction.[5,6]

Cerebral arterial vasospasm, in contrast, is defined as focal or diffuse temporary narrowing of the vessel caliber due to contraction of the arterial wall smooth muscle as detected on, or inferred from, imaging studies (eg, DSA, transcranial Doppler, CT, or MR imaging) or as seen during surgical clipping.[7] Vasospasm was long thought to be the sole cause of DCI, leading to an overlap in historical definitions. However, not all patients with angiographic vasospasm meet the clinical criteria for DCI, and most do not develop infarcts.[4,8] Therefore, prevention of vasospasm does not necessarily reduce the incidence of DCI:[4,8] Recent literature suggests that DCI has a multifactorial pathogenesis, including microvascular spasm, microthromboses, vascular dysregulation, breakdown of the blood-brain barrier, and cortical spreading depolarization.[4,9] Vasospasm is now preferentially used to describe imaging findings, with "symptomatic vasospasm" now more accurately referred to as DCI when it meets the clinical criteria.[3]

There is wide practice variation with respect to surveillance for vasospasm, with institutions relying on a combination of serial clinical examination, transcranial Doppler ultrasonography, CTA, CTP, and DSA to predict and diagnose DCI and vasospasm. In particular, CTP has demonstrated promise in the early prediction and diagnosis of both vasospasm and DCI.[8,10]

The purpose of this systematic review and meta-analysis was to pool diagnostic test accuracy metrics for CTP detection of DCI and vasospasm compared with the established reference standard definitions of clinical DCI or delayed infarct and DSA, respectively.

MATERIALS AND METHODS

Search Strategy and Information Sources

The search strategy was devised in accordance with the revised Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and registered with PROSPERO (CRD42021288313; https://www.crd.york.ac.uk/PROSPERO/).[11,12] Electronic searches were performed using the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Clinical Answers, Cochrane Methodology Register, Ovid MEDLINE, EMBASE, American College of Physicians Journal Club, Database of Abstracts of Reviews of Effects, Health Technology Assessment, National Health Service Economic Evaluation Database, PubMed, and Google Scholar from their inception to September 2023. Search terms included ["subarachnoid hemorrhage"] AND ["brain ischemia" OR "delayed cerebral ischemia" OR "vasospasm"] AND ["CT" OR "CT perfusion" or "perfusion imaging"] inclusive of relevant Medical Subject Headings terms or keywords, with US and UK spelling variations. Articles published between database inception to September 20, 2023, were included, without language restrictions. Following removal of duplicate studies, title and abstract screening was performed by 2 reviewers (V.V.G. and A.M.). Discrepancies were resolved by the senior investigators (M.V.C. and M.A.). Full texts were obtained, and their reference lists were reviewed to identify further relevant studies.

Selection Criteria

We included prospective and retrospective studies that published diagnostic test accuracy statistics regarding CTP performed at any time following aSAH. These encompassed studies for prediction (ie, performed within 72 hours of onset of aSAH or without deterioration) or for detection of DCI or vasospasm. Studies aiming to predict rather than detect DCI were included to capture a potential continuum between instigating factors (eg, microcirculatory dysfunction) and DCI. The reference standard for DCI was the clinical diagnosis of DCI or radiologic infarct, as per the established definition.[3] For vasospasm, luminal narrowing on conventional (digital subtraction) angiography was the reference standard. When accuracy was reported by perfusion metrics, time, or on an ROI basis, these were extracted and considered for subanalysis. To avoid duplication of cohorts, we scrutinized studies with the risk of overlapping cohorts and included the most complete data set. We excluded studies with non-aSAH, <20 patients, or in which diagnostic test accuracy data were not extractable. Abstracts, case reports, case series, conference presentations, editorials, review articles, and prior systematic reviews and meta-analyses were also excluded. The search strategy and selection process are summarized graphically per the PRISMA guidelines.[11]

Data Extraction and Critical Appraisal

All data were extracted from article texts, tables, and figures. Two investigators (V.V.G. and A.M.) independently extracted data including study design, patient demographics, study inclusion and exclusion criteria, cohort enrollment, CTP timing following ictus, CTP technique, reference standard, and diagnostic test accuracy data (true- and false-positives and -negatives, sensitivity, specificity, and positive and negative predictive values). When multiple diagnostic parameters were reported, we recorded all of these to facilitate subgroup analyses. Published data on transcranial Doppler for prediction of DCI was used as a comparator to define sensitivity and specificity of <70% as "low," 70%–85% as "moderate," and >85% as "high."[13]

Discrepancies between the 2 reviewers were resolved by discussion and consensus, and the results were reviewed by the senior investigator (M.V.C.). To minimize the risk of bias due to missing results, we made to an effort to contact all corresponding authors of potential articles in which data (such as 2 × 2 tables) were not available.[14] The risk of bias in the included studies was assessed using the Quality Assessment of Diagnostic Accuracy of Studies (QUADAS-2; https://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/) tool.[15] Standardized

questions from the QUADAS-2 about patient selection, index test, reference standard, flow, and timing were performed by the 2 investigators (V.V.G. and A.M.). A conservative approach was used overall, with a "high" risk of bias used for any question within a domain rated "no" and "uncertain" if a question was not clearly answered.

Perfusion Parameters

Studies were not excluded on the basis of specific perfusion parameters used to demonstrate the marked heterogeneity in the assessment in the literature. Data included whether absolute or relative parameters were recorded, such as relative CBF (rCBF) and relative CBV (rCBV), in which case normalization of tissue perfusion was performed. In these cases, normalization was either to a contralateral ROI, or, more recently, such as in the case of RApid processing of PerfusIon and Diffusion (RAPID; iSchemaView) software, normalization was performed by dividing the CBF within a voxel by the median CBF of the patient's normally perfused tissue.[16] Most included articles used absolute threshold values, obtained by scaling using a venous outflow function. Qualitative analysis of CTP or nonconventional methods such as a derived circulation time were also included. The perfusion software, algorithm, and tracer-delay sensitivity have been collected in the Online Supplemental Data. Reported perfusion parameters have been summarized in the Online Supplemental Data. The synthesis of all perfusion parameters within this article represents the notable changes in CTP processing since inception, with the introduction of some parameters after the publication of several large included studies.

Statistical Analysis

Statistical analysis was performed using Meta-DiSc 2.0 (https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-022-01788-2), a Web-based application using the R-shiny software package (https://shiny.posit.co/r/getstarted/shiny-basics/lesson1/index.html).[17] A 2-tailed P value $<$ .05 was considered statistically significant. The Meta-DiSc 2.0 analysis used a bivariate random effects regression model via the glmer function of the lme4 package (https://www.rdocumentation.org/packages/lme4/versions/1.1-35.3/topics/glmer), allowing correlation between sensitivity and specificity.[17] A minimum of 4 studies was required for pooling or subgroup analysis. A bivariate model was selected, and assessment of the relative sensitivity and specificity and their statistical significance was by means of the lmtest package (https://cran.r-project.org/web/packages/lmtest/index.html).[17] Results were presented as summary sensitivities, specificities, likelihood ratios (LRs), and receiver operating characteristic area under the curve values with 95% CIs. Positive LRs of 5–10 and $>$10 were considered moderate and strong diagnostic evidence, respectively. Similarly, negative LRs of 0.1–0.2 and $<$0.1 were considered moderate and strong diagnostic evidence, respectively.[18]

RESULTS

A total of 1510 references were identified through 12 electronic database searches, of which 82 articles met criteria for full-text review. Manual search through reference lists did not yield additional relevant studies. After we applied the selection criteria, 30 studies were included in this meta-analysis with 19 assessing DCI, 8 assessing vasospasm, and 3 assessing both (Fig 1). Of the selected articles, 19 were prospective[19-37] and 11 were retrospective (Online Supplemental Data).[38-48] Twelve studies were primarily intended to predict DCI/vasospasm, 15 were primarily intended to detect the entities, and 3 were intended to do both (Online Supplemental Data). A total of 1786 patients were included, with an age range of 18–87 years, 66.5% of whom were women. A total of 2302 CTP studies were included. A summary of the included studies, patient baseline characteristics, and CTP techniques are presented in the Online Supplemental Data. For DCI subgroup analysis, data from 12 articles could be pooled for CBF, 7 for CBV, 12 for MTT, 8 for TTP, and 4 for time-to-maximum (Tmax). For vasospasm, CBF values were pooled from 5 studies.

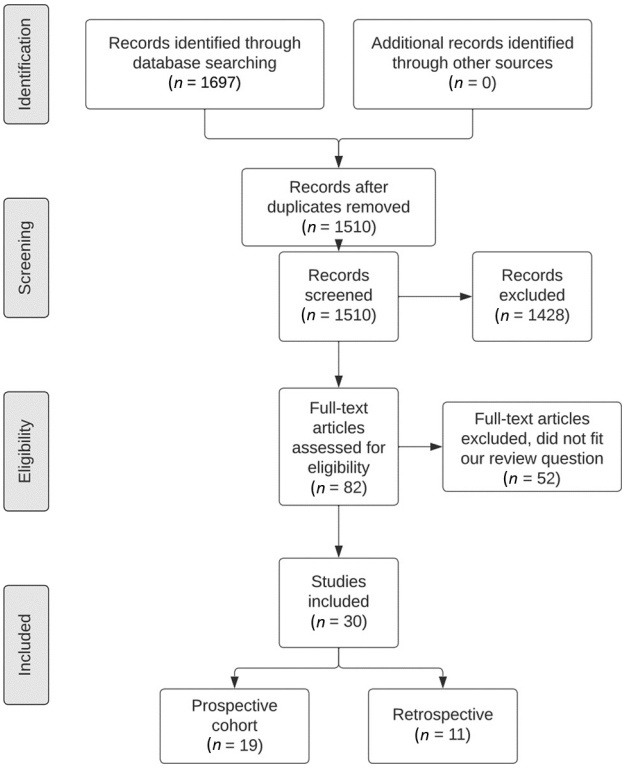

FIG 1. PRISMA flow chart.

Twenty-five studies used quantitative methods, and 5 studies used qualitative methods (Online Supplemental Data). When reported, most studies used tracer-delay–insensitive algorithms to generate CTP metrics, though many articles did not specify the algorithm or tracer-delay sensitivity of their methods (Online Supplemental Data). The prevalence of DCI, aneurysm location, and treatment modalities is summarized in the Online Supplemental Data.

Quality Assessment of Trials

Structured assessment of potential study bias using the QUADAS-2 tool is presented in the Online Supplemental Data. Twelve included studies were deemed to have a low risk of bias and had no applicability concerns. There were 11 studies deemed to have medium risk and 7 deemed to have a high risk of bias. The index test domain was most commonly deemed a high risk

of bias (Fig 2; 30%) when threshold values for CTP were not prospectively specified before interpretation. Failure to prospectively define the threshold criteria may overestimate the index test performance. Flow- and timing-related bias was considered high when DCI was diagnosed within too-short an interval (<48 hours) or when the reference standard was inconsistently applied. We considered articles at high risk of bias related to the reference standard if readers were not clearly blinded to the CTP outcome during determination of DCI or when infarct and DCI were determined during the same examination.

Diagnostic Assessment of DCI

The diagnostic accuracy of CTP for assessment of DCI was reported in 22 studies, with a pooled sensitivity of 82.1% (95% CI, 74.5%–87.8%), specificity of 79.6% (95% CI, 73.0%–84.9%), positive LR of 4.01 (95% CI, 2.94–5.47), and negative LR of 0.23 (95% CI, 0.12–0.33) (Table 1).

The most sensitive CTP parameter was TTP, reported in 7 studies with a pooled sensitivity of 82.2% (95% CI, 71.4%–89.5%) and specificity of 70.6% (95% CI, 59.2%–79.9%). The parameter with the highest positive LR was CBF, reported in 12 studies, with a positive LR of 4.62 (95% CI, 3.12–6.84). Pooled assessment of MTT was performed in 12 studies, showing a sensitivity of 80.7% (95% CI, 73.3%–86.5%) and specificity of 69.3% (595% CI, 61.4%–76.2%). Pooled assessment of Tmax revealed a sensitivity of 63.8% (95% CI, 52.5%–73.8%) and a specificity of 81.5% (95% CI, 72.5%–88.1%).

Subgroup Analysis for DCI

Subgroup analysis could be performed on 6 studies for the evaluation of the sensitivity between an MTT of 84.3% (95% CI, 76.9%–89.7%) and CBV of 70.6% (95% CI, 63.0%–77.2%) ($P = .009$) (Table 2).

However, specificity and the diagnostic OR in these studies were not statistically significant. Five studies included the timing of CTP performed, allowing accuracy data to be pooled with a 72-hour cutoff. This result showed a trend toward greater sensitivity at later timepoints, 84.5% (95% CI, 57.3%–95.7%) versus 55.8% (95% CI, 27.3%–80.8%), but it was not statistically significant ($P = .11$, Table 2).

Diagnostic Assessment of Vasospasm

The diagnostic accuracy of CTP for the assessment of vasospasm was performed in 11 studies, with a pooled sensitivity of 85.6% (95% CI, 74.2%–92.5%), specificity of 87.9% (95% CI, 79.2%–93.3%), a positive LR of 7.10 (95% CI, 3.87–13.04), and a negative LR of 0.16 (95% CI, 0.09–0.31) (Table 1). Pooled bivariate analysis could be performed on CBF only, which was reported in 5 studies with a sensitivity of 60.9% (95% CI, 45.0%–74.7%), specificity of 92.2% (95% CI, 80.7%–97.1%), a positive LR of 7.83 (95% CI, 3.06–20.06), and a negative LR of 0.42 (95% CI, 0.29–0.62).

DISCUSSION

This meta-analysis and systematic review demonstrates moderate sensitivity and specificity for DCI (82.1% and 79.6%, respectively) and vasospasm (85.6% and 87.9%). Furthermore, MTT was more sensitive than CBF for detecting DCI (84.3% versus 70.6%, $P = .009$). These results suggest that CTP may be useful as a noninvasive adjunct test for the diagnosis of DCI and vasospasm, but it may not be sufficiently accurate for use in isolation.

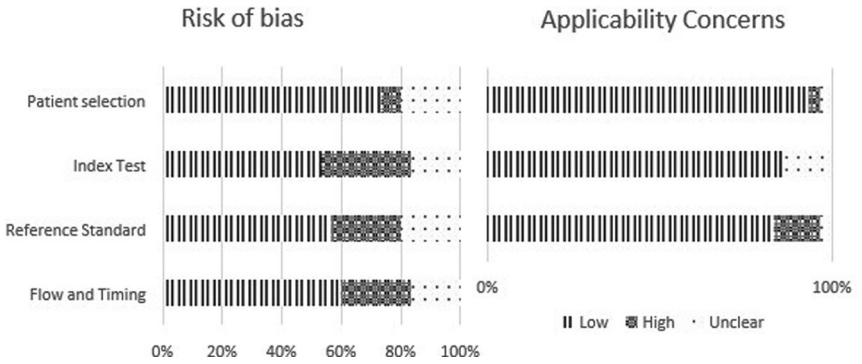

FIG 2. Risk of bias and applicability concerns by QUADAS-2 domain.

CTP Acquisition Technique, Parameters, and Postprocessing

There was heterogeneity of CTP techniques among the included studies, which limits comparability and may confound the assessment of optimal parameters for detecting DCI and vasospasm. Variability may be due to the model and generation of the CT scanner, contrast bolus and delivery, processing software, institutional optimization, and may be compounded by improvements

Table 1: Pooled analyses for CTP and subparameters for detection of vasospasm and delayed cerebral ischemia

	Studies	Pooled Sensitivity (%) (95% CI)	Pooled Specificity (%) (95% CI)	Positive LR	Negative LR	Diagnostic OR
Vasospasm						
CTP	11	85.6 (74.2–92.5)	87.9 (79.2–93.3)	7.10 (3.87–13.04)	0.16 (0.09–0.31)	43.41 (14.4–130.49)
CBF	5	60.9 (45.0–74.7)	92.2 (80.7–97.1)	7.83 (3.06–20.06)	0.42 (0.29–0.62)	18.47 (6.16–55.38)
DCI						
CTP	22	82.1 (74.5–87.8)	79.6 (73.0–84.9)	4.01 (2.94–5.47)	0.23 (0.12–0.33)	17.79 (9.66–32.76)
CBF	12	73.5 (62.0–82.4)	84.1 (77.1–89.3)	4.62 (3.12–6.84)	0.31 (0.32–0.47)	14.64 (7.58–28.25)
CBV	7	64.3 (50.6–75.9)	73.9 (60.1–84.1)	2.46 (1.72–3.52)	0.48 (0.37–0.64)	5.08 (3.16–8.17)
MTT	12	80.7 (73.3–86.5)	69.3 (61.4–76.2)	2.63 (2.04–3.39)	0.28 (0.20–0.40)	9.46 (5.49–16.29)
TTP	7	82.2 (71.4–89.5)	70.6 (59.2–79.9)	2.79 (1.91–4.09)	0.25 (0.15–0.43)	11.06 (4.85–25.20)
Tmax	4	63.8 (52.5–73.8)	81.5 (72.5–88.1)	3.45 (2.44–4.88)	0.44 (0.34–0.57)	7.77 (5.00–12.09)

Table 2: Pooled subgroup analysis and metaregression for CTP for detection of delayed cerebral ischemia

	Studies	Pooled Sensitivity (%) (95% CI)	Pooled Specificity (%) (95% CI)	Positive LR	Negative LR	Diagnostic OR
CTP <72 hr	5	55.8 (27.3–80.8)	93.7 (66.8–99.1)	8.81 (1.12–68.38)	0.47 (0.23–0.96)	18.0.66 (1.45–239.63)
CTP >72 hr	5	84.5 (57.3–95.7)	84.9 (48.0–97.2)	5.60 (1.14–27.60)	0.18 (0.05–0.65)	30.73 (2.50–378.08)
	Relative sensitivity >72 hr vs <72 hr = 1.52 (95% CI, 0.85–2.68); P = .11; relative specificity >72 hr vs <72 hr = 0.91 (95% CI, 0.67–1.22); P = .47					
MTT threshold	5	75.4 (61.6–85.4)	66.6 (51.3–79.0)	2.25 (1.33–3.81)	0.37 (0.20–0.69)	6.10 (1.98–18.78)
MTT qualitative	5	67.9 (56.9–85.9)	78.8 (69.2–85.9)	3.19 (2.09–4.89)	0.41 (0.29–0.57)	7.86 (3.92–15.76)
	Relative sensitivity threshold vs qualitative = 1.14 (95% CI, 0.92–1.40); P = .24; relative specificity threshold vs qualitative = 0.82 (95% CI, 0.66–1.02); P = .10					
CBF	7	74.1 (60.8–84.1)	87.4 (75.1–94.2)	5.91 (2.99–11.67)	0.30 (0.20–0.45)	19.96 (8.99–44.32)
CBV	7	64.3 (50.6–75.9)	73.9 (60.1–84.1)	2.45 (1.72–3.52)	0.48 (0.37–0.64)	5.08 (3.16–8.17)
	Relative sensitivity CBV vs CBF = 0.88 (95% CI, 0.69–1.12); P = .30; relative specificity CBV vs CBF = 0.86 (95% CI, 0.70–1.05); P = .13					
CBF	8	78.9 (72.7–84.0)	79.6 (64.7–89.3)	3.87 (2.11–7.10)	0.27 (0.19–0.36)	14.62 (6.38–33.49)
MTT	8	81.5 (73.5–87.5)	79.2 (69.9–86.2)	3.91 (2.68–5.71)	0.23 (0.16–0.34)	16.77 (9.31–30.22)
	Relative sensitivity MTT vs CBF =1.03 (95% CI, 0.93–1.14); P = .64; relative specificity MTT vs CBF = 1.02 (0.85–1.23); P = .85					
CBV	6	70.6 (63.0–77.2)	68.5 (59.9–75.9)	2.24 (1.72–2.91)	0.43 (0.33–0.56)	5.21 (3.24–8.40)
MTT	6	84.3 (76.9–89.7)	74.4 (66.7–80.9)	3.30 (2.43–4.47)	0.21 (0.14–0.33)	15.64 (8.03–30.46)
	Relative sensitivity MTT vs CBV = 1.182 (95% CI, 1.05–1.33); P = .009; relative specificity MTT vs CBV = 1.09 (95% CI, 0.94–1.25); P = .27					

in CTP techniques since these have entered mainstream use for evaluation of ischemic stroke.[49]

Z-axis spatial resolution is primarily dependent on the number of detectors in the multidetector CT array, which has progressively increased with newer scanner technology.[50] For example, the earliest studies included in our meta-analysis used 8-,[47] 16-,[51] or 64-detector[36] CT scanners, with scan ranges between 20 and 40 mm, whereas the most recently included study used a 256-detector CT scanner with a scan range of 160 mm.[37] Thus, the volume of brain parenchyma interrogated has increased with newer scanners and may confound pooled results.

Acquisition times for CTP within the included studies ranged between 20 and 60 seconds, with temporal sampling intervals between 0.5 and 4.5 seconds. Shorter imaging times risk obtaining an incomplete concentration of tissue curve in patients with poor cardiac output, atrial fibrillation, and carotid stenoses,[50] whereas increasing temporal sampling intervals has been shown to overestimate rCBF, rCBV, and TTP and underestimate MTT in the context of ischemic stroke.[52]

Comparison of commonly available software packages is known to demonstrate substantial variations in perfusion indices in the context of ischemic stroke.[53,54] An in-depth review of these algorithms is beyond our scope but is well-described elsewhere.[49,50] Tracer-delay sensitivity is thought to play an important role in accounting for such differences in vitro and in vivo.[53] Delay-sensitive models such as the maximum slope technique are reliant on accurate timing information and are prone to error when there is a delay or dispersion of the arterial input function. In contradistinction, delay-insensitive models such as block-circulant singular value decomposition are less susceptible to timing bolus delays.[49] At least 1 study found that both delay-sensitive and insensitive algorithms have similar performance for the detection of DCI in the setting of aSAH.[55] However, the reporting of CT perfusion algorithms or time-delay sensitivity was very poor among included articles, limiting meaningful comparison between studies.

Delayed Cerebral Ischemia

Overall, CTP has a reasonable sensitivity for the diagnosis of DCI when pooling the best metric reported by individual studies. The most sensitive individual parameter for DCI was found to be a TTP at 82.2% (95% CI, 71.4%–89.5%), differing only slightly from MTT, demonstrating a sensitivity of 80.7% (95% CI, 73.3%–86.5%). The most specific parameter was found to be CBF.

TTP measures the time taken for contrast concentration to reach the maximum value within an ROI. It does not differentiate the cause a prolonged time and is influenced by any cause of delayed arrival of the injected contrast bolus. Causes of increased TTP include a poor bolus injection rate, poor cardiac output, and proximal (eg, proximal carotid) steno-occlusive disease. In the setting of medium vessel vasospasm in SAH, a prolonged TTP is expected due to the proximal delay of blood flow. While the underlying etiology of DCI remains uncertain, microvascular thrombosis at the capillary level may be a distal cause of prolonged TTP.

MTT, however, reflects the time taken for contrast to traverse the tissue capillary bed, and determination of MTT requires the use of delay-insensitive deconvolution. When delay-sensitive deconvolution is used, the MTT obtained is also affected by the delay in the arrival of contrast to the tissue voxel (ie, Tmax), explaining why early studies found MTT to be the optimal parameter in predicting penumbra.[56] If one assumes that DCI is a microvascular/capillary phenomenon rather than due to macrovascular spasm, MTT should be the most sensitive parameter. In the included articles, there is underreporting of the exact parameter calculation techniques, including the use of delay-insensitive deconvolution, possibly leading to a biased result. If delay-

sensitive techniques have been used but not reported, MTT no longer accurately represents capillary transit time. In contradistinction, TTP is far less susceptible to calculation technique–based variability. Possibly, the supremacy of TTP in the current study reflects the heterogeneity of the calculation technique rather than a true superiority.

While the meta-analysis suggests that CTP shows a promising sensitivity for DCI detection, one must consider the highly-selected patient cohort represented in the pooled studies.

Given the inherent risk of DCI and vasospasm among patients with aSAH, a sensitivity of 82.2% for TTP may not be high enough to meaningfully alter clinical practice. However, CTP could prove beneficial in scenarios in which clinical assessment is hindered, for example by sedation, electrolyte disturbances, or hydrocephalus. Despite the encouraging sensitivity, the low negative LR of 0.23 (95% CI, 0.12–0.33) for DCI necessitates cautious interpretation of negative results on CTP. A negative finding on CTP should not dissuade treatment if there is a strong index of suspicion for DCI on clinical grounds. Integrating clinical features, CT brain and angiogram findings, along with CTP results, could potentially enhance the overall diagnostic accuracy, but further research is warranted to definitively support this approach.

Tmax, defined as the time to the maximum of the tissue residue function after deconvolution, represents the delay between the arterial input function and the contrast arrival time in the tissue voxel. This delay is influenced by arterial stenosis or occlusion proximal to the voxel, including proximal arterial stenoses or occlusions, reduced cardiac output, and bolus dispersion. These may delay and broaden the arterial input function, leading to a prolonged Tmax. The deconvolution process does not completely account for all delays. The complexity of the effect of bolus dispersion on Tmax and the impact of the regularization process in deconvolution, which causes the Tmax to shift to later time points, are crucial considerations in interpreting Tmax values. Additionally, MTT also has a mild influence on Tmax.

Although Tmax has recently been recognized as the most sensitive predictor of tissue-at-risk for ischemic stroke,[38,57] few articles have reported its utility in the context of aSAH. In DCI, the underlying pathophysiology is suspected to be at the capillary level and should therefore affect Tmax, which reflects macrovascular (arterial) transit, less so than MTT, which reflects microvascular transit. The parameter is, however, expected to be a marker for vasospasm, for which insufficient articles were identified to permit analysis.

Quantitative versus Semiquantitative Measures

There was heterogeneity in the methods of interpretation of CTP, particularly in defining DCI. Some studies rely on a subjective visual assessment by a neuroradiologist, while others use absolute threshold values. Another commonly used method is rCBF, which compares blood flow in a specific brain region with the blood flow in a normalized reference region, commonly the contralateral hemisphere. This method enables comparisons between different brain regions and individuals, in contrast to routine CBF, which provides only absolute blood flow in a specific brain region.

There is no consensus regarding which absolute CTP parameter or value should be used for the diagnosis of DCI. Varied reporting methods limit pooling for meta-analysis so that standardization is needed—similar to the application of this technology in acute stroke. Of the studies included, 5 allowed direct subgroup analysis among threshold values.

Our results show that the threshold values had higher sensitivity and lower specificity than semiquantitative measures of MTT; however, the results were not statistically significant.

Timing of CTP

There was a wide range of reported timing of CTP following aSAH ictus. This is partly due to early studies examining its predictive value for DCI in the first 24 hours,[51] before symptom onset, and subsequent studies assessing the diagnostic value, which is dependent on symptom onset rather than a specific time. A threshold of 72 hours was selected to facilitate pooling of at least 4 studies for comparison. Five studies that clearly defined results on the basis of CTP performed before and after 72 hours could be pooled, showing a trend toward greater sensitivity after 72 hours; however, the results were not statistically significant in the context of a small number of studies. The results suggest that CTP cannot be used confidently within 72 hours of presentation to detect DCI with a sensitivity from 4 studies of 59.9% (95% CI, 27.9%–85.3%). The timing of CTP in relation to vasospasm treatment was also not reported in any study and warrants attention in future studies. With the data available, the effect of endovascular treatment on perfusion parameters cannot be established.

Vasospasm

On the basis of our results, CTP is accurate for the diagnosis of vasospasm. Different methods for measuring CTP in vasospasm detection were used, with some studies measuring predefined ROIs and others assessing the whole brain on a quantitative or semiquantitative basis as with DCI. The pooled analysis demonstrated a higher sensitivity on a per-patient basis rather than at an ROI level.

Limitations

Our systematic review identified heterogeneity in the definitions and terms used for DCI and vasospasm throughout the literature. For example, many studies described the use of DSA as a reference standard for DCI. For purposes of meta-analysis, only articles that conformed to consensus DCI definitions proposed by Vergouwen et al[3] were included, limiting the overall included number of patients. Additionally, the pooled studies were both prospective and retrospective, with varied inclusion criteria and definitions, increasing the risk of bias.

The impact of postadmission variables (such as poor cardiac output, infection, seizures, or method of aneurysm repair) on perfusion results was not specified in most patients. There were relatively small numbers in subgroup analysis, which also contributed to high heterogeneity.

While perfusion test parameters have been collected, correcting these parameters including contrast injection rate, contrast dose, and arterial input function, and ROI placement was not possible. This issue was partly due to the rapid change in CTP technology between the first and most recently included articles and partly due to a lack of standardization of CTP methods

across vendors. Specific factors have been detailed earlier in the Discussion, including variations in CTP acquisition hardware and z-axis resolution, acquisition time, software packages, and postprocessing algorithms, resulting in notable heterogeneity of included data sets. The lack of clarity regarding postprocessing software and deconvolution techniques, including the use of delay-sensitive processes, has limited the assessment of MTT in particular.

Finally, inclusion of studies in which CT perfusion was performed at <72 hours from ictus is likely to have skewed the results toward lower accuracy, due to these studies being aimed at predicting DCI rather than detecting it.

Directions for Future Research

As CTP technology advances, it offers the potential for the diagnosis of DCI and vasospasm in aneurysmal SAH. However, to ensure accurate systematic reviews, future studies should conform to the consensus definition of DCI[3] and report 2 × 2 tables for each perfusion parameter with true-/false-positive values. The specific quantitative or qualitative thresholds used must be reported as well as postprocessing algorithm and tracer-delay sensitivity. A large study using MTT derived using a delay-insensitive deconvolution may provide greater accuracy for both early prediction of DCI and detection of DCI. Given the proved reliability of Tmax in ischemic stroke, it may emerge as a reliable marker of vasospasm; however, it is not necessarily expected to detect DCI.

Reporting the timing of CTP and its relation to endovascular vasospasm treatment is also crucial to better understand the effects of endovascular treatment on cerebral perfusion parameters. A study using standardized software is essential to ensure the comparability of CTP parameters.

CONCLUSIONS

The role of CTP in the diagnosis of both DCI and vasospasm remains limited as an adjunct to the overall clinical presentation. The data suggest that CTP has better performance for the detection of vasospasm than DCI. In subgroups of patients for whom the clinical assessment is unreliable or where transcranial Doppler is not available, CTP offers an alternative noninvasive test to guide or triage management. However, the data presented emphasize the need for standardized definitions, precise reporting of perfusion thresholds and outcomes, and standardized CTP parameters by vendors.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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