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VIEWS AND REVIEWS

# Arterial spin labeling compared to dynamic susceptibility contrast MR perfusion imaging for assessment of ischemic penumbra: A systematic review

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## Abstract

**Background and Purpose:** Dynamic susceptibility contrast (DSC) MR imaging is commonly used to estimate penumbra size in acute ischemic stroke; this technique relies on the administration of gadolinium contrast, which has limited use in certain populations, such as those with impaired renal function or allergies. Arterial spin labeling (ASL) is a relatively new technique that can provide information on cerebral perfusion without need for exogenous contrast agents. This systematic review examines published studies that specifically compared ASL to DSC for assessment of ischemic penumbra.

**Methods:** We searched PubMed, Embase, Web of Science, and the Cochrane Library for papers which compared ASL with DSC for assessment of ischemic penumbra in acute ischemic stroke among adult human populations. Two independent reviewers screened studies using predefined inclusion and exclusion criteria. Study characteristics and findings regarding the utility of ASL compared to DSC for identification of penumbra were then extracted and anlyzed for results and risk of bias.

**Results:** Seventeen articles met inclusion and exclusion criteria. Studies compared ASL with DSC on a range of metrics (hypoperfusion, hyperperfusion, mismatch, and reperfusion). Most studies concluded that agreement of ASL with DSC was moderate to very high. A small subset of studies found discrepancy in agreement of ASL with DSC for size or location of perfusion abnormalities. *A heterogeneity of perfusion parameters studied for DSC was noted, along with the need for more standardization of research methods.*

**Conclusion:** ASL shows moderate to high agreement with DSC for detection of penumbra among ischemic stroke patients.

KEYWORDS
gadolinium, ischemia, magnetic resonance imaging, perfusion imaging, stroke

## INTRODUCTION

The severity of cerebral perfusion impairment varies across the vascular territory affected in ischemic stroke. The ischemic core, characterized by irreversible injury, will exhibit a severe perfusion deficit, whereas surrounding regions, often termed ischemic penumbra, are characterized by lesser degrees of impaired perfusion, which do not cause immediate irreversible injury, but pose the risk of extension of the infarct core. Because the penumbra represents tissue experiencing less severely impaired perfusion, it is associated with higher likelihood of tissue salvage.[1] One of the goals of acute stroke treatment is to reduce hypoxic injury by restoring or improving perfusion

  

to ischemic regions.[2] Imaging may allow noninvasive assessment of ischemic penumbra, which may be helpful in the assessment of risk and planning of intervention.[2]

Several imaging methods have been developed to measure cerebral perfusion, including single photon emission computed tomography with $^{99m}$Tc-Hexamethylpropylene amine oxime, xenon-CT, and $^{15}$O Positron emission tomography.[3] Two MRI methods for assessment of cerebral perfusion are approved by the Food and Drug Administration and are currently available on standard clinical MRI scanners. Dynamic susceptibility contrast (DSC) MR imaging is a first-pass technique that entails rapid imaging during the injection of a bolus of a gadolinium-based contrast agent (GBCA). Concerns regarding the safety of GBCAs may limit the use of this technique in certain patient populations, such as patients with poor renal function[4] or allergies.[5] Moreover, the need for the GBCA limits repetition of the DSC measurement and increases cost. Arterial spin labeling (ASL) is a new MRI technique that quantifies cerebral perfusion by magnetically labeling blood water protons, without the need to administer an exogenous contrast agent.

The aim of this systematic review is to determine whether the existing literature supports ASL as equivalent to DSC for assessment of ischemic penumbra.

## METHODS

### Search strategy

Two medical librarians designed and executed searches of PubMed, Embase (1971–2021), Web of Science (1985–2021), and the Cochrane Library to identify all English language articles comparing ASL to DSC in the assessment of acute ischemic stroke in humans.

Search terms were as follows: spin labels, arterial spin labeling, arterial spin labelling, ASL, diagnostic uses of chemicals, gadolinium, diffusion-weighted imaging (DWI), perfusion weighted imaging, mismatch, bolus tracking perfusion, dynamic susceptibility, exogenous contrast, contrast agent, contrast media, contrast based, contrast enhanced, stroke, and strokes. The following terms were excluded: rodentia, rodent, rat, rats, mouse, and mice. In PubMed, we additionally included *medical subject headings* terms "spin labels," "diagnostic use of chemicals," and "stroke." For the Embase search, Emtree terms, title, and abstract words were searched. A topic search was conducted in the Web of Science. A keyword search was conducted in the Cochrane Library. No date restriction was implemented in the search strategy. Articles retrieved were published from March 1997 to February 2021. Electronic search strategies for the databases are available upon request. The authors declare that all supporting data are available upon request. *The authors followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in this systematic review. The protocol has not been registered in any platform.*

### Selection criteria

After removingduplicates from the search results, article titles and abstracts were reviewed independently by two investigators for the following criteria: (1) human study comparing ASL to DSC, (2) cases of acute stroke only (not transient ischemic attack, chronic stroke, etc.), (3) human patients aged 18 and older, and (4) full articles and English language publication. Exclusion criteria included: animal studies, patients <18 years, case-reports, reviews, not an ASL/DSC comparison, nonstroke related, ongoing trial/not yet published, and only abstract available. Next, the two investigators compared their screening results and reached a consensus on any disagreement regarding inclusion status. Articles included based on this first round of screening underwent a second round of screening, where the investigators each reviewed the main text of the included articles, employing the same criteria and methods as in the title/abstract review.

### Data extraction and outcomes of interest

For the selected studies, the following variables were extracted by two investigators: stroke characteristics, publication year, number of male and female subjects, mean age, magnetic field strength, perfusion MR technique, perfusion parameters assessed, whether image quality was reported, and the statistical tests used to compare ASL with DSC as well as the results of the analyses. These tasks were divided between the two investigators.

For studies that used correlation as the statistical technique to compare ASL with DSC, we rated the correlation coefficient as "low," "moderate," "high," or "very high" based on Mukaka's guidelines.[7] For studies that only reported whether ASL and DSC detected the presence or absence of mismatch or hypoperfusion, we reported percent agreement. For studies that reported percent agreement or area under the curve, we rated the values as "no discrimination," "acceptable," "excellent," and "outstanding," according to Mandrekar's guidelines.[8] When studies compared ASL to DSC using the Wilcoxon signed rank test or paired *t*-test, the results were characterized as either "comparable" or "not comparable." Where studies reported on more than one DSC parameter, we assessed the DSC parameter that achieved the highest correlation with ASL.

In order to assess the risk of bias in the selected articles, two investigators divided the work to record sample size and sex ratio for each study, documented whether image quality and the assessment of inter-rater reliability were reported, and assessed subjectivity in the reporting of results. We also assessed each paper to determine the potential for missing information and publication bias. *When faced with missing information, the authors would perform a search of online supplementary materials before the information was assumed not to be reported. The investigators also double checked each other's tasks.*

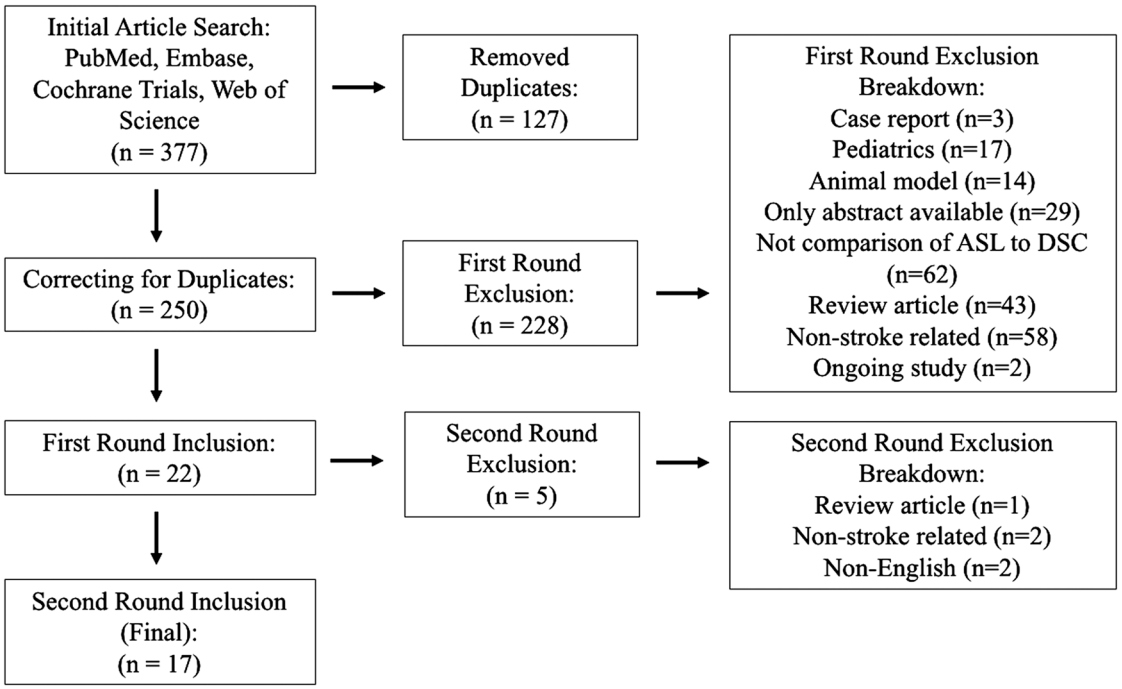


**FIGURE 1** Flow diagram indicating the number of records identified from databases, number of duplicates removed, number of records included and excluded, as well as reasons for exclusions
Abbreviation: *n*, number

## RESULTS

### Studies and participants

The initial search yielded 250 articles, after removing duplicates. After full-text review, 17 articles remained and are included in the analysis. A detailed summary of excluded articles as well as reasons for exclusion is presented in Figure 1.

The 17 articles are composed of retrospective and prospective cohort studies. The study characteristics are presented in Table 1. Two studies had sample sizes of a 100 or more,[9,10] while the remaining studies ranged from sample sizes of 15–58 (Table 1). The mean ages of patients across the studies ranged from 52 to 79.7.

Stroke characteristics are presented in Table 2. The included studies reported on cases of arterial ischemic stroke only, with almost all studies limited to cases of large vessel occlusion. Three studies included lacunar strokes[6,11,12] and two included watershed stroke.[13,14] Ischemic stroke was generally classified by the affected vascular territory.[13–19] Two studies classified stroke based on mechanism (e.g., occlusion, embolism, and dissection).[4,5] One study classified patients based on anatomic territory (e.g., cortical vs. deep gray matter).[12] Four studies used vascular territory along with either infarct territory or etiology.[6,11,20,21] Three studies did not report specific characteristics of the ischemic strokes.[9,10,22] Anterior circulation strokes due to large vessels were by far the most common (Table 2). Strokes involving cortical gray matter were more commonly reported than other regions (Table 2).

### Imaging characteristics

For ASL, the most common perfusion MR technique reported was pseudocontinuous ASL, used in 10 out of 17 studies[10–12,14,15,17,19–22] (Table 1). Other ASL perfusion MR techniques reported to include pulsed ASL and pulsed continuous ASL (Table 1). Perfusion parameter choice was very consistent for ASL studies; all studies primarily reported cerebral blood flow (CBF), with the exception of Wolf et al., who also reported bolus arrival time[4] and Wang et al., who also reported arterial transit time[19] (Table 1).

For DSC, the perfusion parameters reported varied greatly across studies. Some studies reported only one DSC perfusion parameter, while others reported up to four perfusion parameters[9,11,19] (Table 1). The DSC perfusion parameters used include CBF by 10 studies,[4,6,9,11,12,14,19–22] cerebral blood volume (CBV) by three studies,[9,11,19] mean transit time (MTT) by eight studies,[4,9,11,12,15–17,19] and time to peak (TTP)/time to maximum ($T_{max}$) by 11 studies[5,6,9–11,14–16,18–20] (Table 1). Five studies reported the DSC timed threshold (e.g., $T_{max}$ >6 s) used during imaging.[5,16–18,20]

The hemodynamic manifestations on which ASL and DSC were compared were characterized by the papers as hypoperfusion, hyperperfusion, reperfusion, and diffusion–perfusion mismatch. Figure 2 shows an example of ASL and DSC scans detecting hypoperfusion and penumbra in diffusion–perfusion mismatch.[22] Eight studies compared ASL to DSC by measuring volume of perfusion abnormalities,[6,9,15–18,20,21] eight studies assessed the mean hemodynamic parameter value from specified regions of interest,[4,11–14,19,21,22] and one study assessed both.[10]

**TABLE 1** Study characteristics, design characteristics, and findings of ASL versus DSC

| | Sample size | T | Perfusion MRI technique | | Perfusion parameters | | Design characteristics | Findings/best parameter correlation | Rating |
|---|---|---|---|---|---|---|---|---|---|
| | | | ASL | DSC | ASL | DSC | ASL/DSC parameter | | |
| Lee et al.[14] | 32 | 3.0 | Pseudo | 0.1 mmol/kg<br>3.5 ml/s | CBF | CBF, TTP | Hypoperfusion (*) | $r = 0.82$<br>N/A | High |
| Zhang et al.[12] | 30 | 3.0 | Pseudo | 0.1 mmol/kg<br>3 ml/s | CBF | CBF, MTT | Hypoperfusion (M) | $r = -0.531$<br>ASL CBF, DSC MTT | Moderate |
| Wolf et al.[4] | 36 | 1.5 | Pulsed | 0.1 ml/kg<br>3 ml/s | CBF, BAT | CBF, MTT | Hypoperfusion (M) | $r = -0.489$<br>ASL CBF, DSC MTT | Low |
| Mirasol et al.[15] | 24 | 3.0 | Pseudo | 0.1 mmol/kg<br>5 ml/s | rCBF | MTT, TTP | Reperfusion (V) | $k = 0.8$<br>ASL rCBF, DSC MTT/TTP | High |
| Bivard et al.[16] | 58 | 3.0 | Pulsed | Not reported | CBF | MTT, $T_{max}$ | Mismatch (V) | $r^2 = 0.73$<br>ASL CBF threshold 40% DSC $T_{max}$>6 s | Strong |
| Nael et al.[20] | 41 | 1.5 or 3.0 | Pseudo | 0.1 mmol/kg<br>5 ml/s | CBF | CBF, TTP, $T_{max}$ | Hypoperfusion (V)<br>Mismatch (V)<br>Reperfusion (V) | $r = 0.83$<br>ASL CBF, DSC TTP<br>$r = 0.95$<br>ASL CBF, DSC TTP<br>$r = 0.46$<br>ASL CBF, DSC $T_{max}$>6 s | High<br>Very high<br>Low |
| Niibo et al.[17] | 23 | 3.0 | Pseudo | Not reported | CBF | MTT | Hypoperfusion (V)<br>Mismatch (V) | $r = 0.97$ ASL CBF<20 ml/100 g min, DSC MTT>10 s<br>100% ASL CBF<20 ml/100 g min, DSC MTT>10 s | Very high<br>Outstanding |
| Huang et al.[18] | 39 | 3.0 | Pulsed | 0.2 mmol/kg<br>Rate: Not reported | CBF | $T_{max}$ | Hypoperfusion (V) | $r = 0.82$<br>ASL CBF, DSC $T_{max}$>5 s | High |
| Wang et al.[19] | 24 | 1.5 or 3.0 | Pseudo | 0.1 mmol/kg<br>Rate: Not reported | CBF, CBV, ATT | CBF, CBV, $T_{max}$, MTT | Hypoperfusion (M) | $r = 0.70$<br>ASL CBF, DSC CBF | Moderate |
| Nael et al.[21] | 25 | 1.5 or 3.0 | Pseudo | 0.1 mmol/kg<br>5 ml/s | rCBF | rCBF | Hypoperfusion (M)<br>Reperfusion (M) | $t$-test, $p$>0.05<br>$t$-test, $p = 0.01$ | Comparable<br>Not comparable |
| Zaharchuk et al.[5] | 43 | 1.5 | Pulsed continuous | 0.1 mmol/kg<br>4 ml/s | CBF | $T_{max}$ | Mismatch (V) | 57% | No discriminate |
| *Bivard et al.[9] | 100 | 3.0 | Not specified | Not reported | CBF | CBF, CBV, MTT, $T_{max}$ | Hypoperfusion (V) | AUC = 0.86<br>ASL CBF, DSC $T_{max}$ | Excellent |

(Continues)

**TABLE 1** (Continued)

| | Sample size | T | Perfusion MRI technique | | Perfusion parameters | | Design characteristics | Findings/best parameter correlation | Rating |
|---|---|---|---|---|---|---|---|---|---|
| | | | ASL | DSC | ASL | DSC | ASL/DSC parameter | | |
| [a]Bokkers et al.[10] | 105 | 3.0 | Pseudo | 0.1 mmol/kg<br>5 ml/s | Not reported | TTP | Hypoperfusion V, M<br>Mismatch V, M | 83%<br>87% | Excellent<br>Excellent |
| Wang et al.[11] | 26 | 1.5 or 3.0 | Pseudo | 0.1 mmol/kg<br>Rate: Not reported | CBF | CBF-r0, CBF-rm, CBV, MTT, $T_{max}$ | Hypoperfusion (M)<br>Hyperperfusion (M) | $\rho = 0.79$<br>ASL CBF, DSC MTT<br>$\rho = 0.668$<br>ASL CBF, DSC MTT | High<br>Excellent |
| Huck et al.[6] | 15 | 3.0 | Pulsed | 0.2 mmol/kg<br>5 ml/s | CBF | rCBF, TTP | Hypoperfusion (V)<br>Mismatch (V) | $r = 0.992$<br>ASL CBF, DSC TTP<br>80%<br>ASL CBF, DSC rCBF | Very high<br>Excellent |
| Hernandez et al.[22] | 28 | 3.0 | Pseudo | Dose: Not reported<br>Rate: 5 ml/s | rCBF | rCBF | Mismatch (M) | Wilcoxon signed rank test and $t$-test, $p>0.5$ | Comparable |
| Siewert et al.[13] | 18 | 1.5 | EPISTAR | 0.1 mmol/kg<br>5 s | Not reported | Not reported | Hypoperfusion (M)<br>Hyperperfusion (M) | Wilcoxon signed rank test, $p>0.05$<br>Wilcoxon signed rank test, $p>0.05$ | Comparable<br>Comparable |

*Note*: This table shows the study characteristics, design, and results of the studies comparing arterial spin labeling (ASL) to dynamic susceptibility contrast (DSC). The principle summary measures through which the studies compared ASL and DSC are presented in this table. The ratings for these measures, such as "no discrimination," "acceptable," "excellent," "outstanding," and so on, were defined according to guidelines from review articles described in the Methods section.

Abbreviations: AUC, area under curve; BAT, bolus arrival time; CBF, cerebral blood flow; CBFr0, CBF based on Time 0; CBFrm, CBF based on $T_{max}$; CBV, cerebral blood volume; EPISTAR, Echo Planar Imaging Signal Tagging with Alternating Radiofrequency; $k$, inter-rater reliability; MTT, mean transit time; N/A, not applicable; Pseudo, Pseudocontinuous; $r$, Pearson's correlation coefficient; rCBF, relative cerebral blood flow; $\rho$, Spearman's correlation coefficient; T, Tesla; $T_{max}$, time to maximum; TTP, time to peak.

[*]V, estimated lesion volume size. [*]M, mean hemodynamic perfusion value from region of interest.

*Bivard et al.[9] described hyperperfusion correlation as strong but did not provide correlation statistics.

[a]Bokkers et al.[10] reported the number of cases where ASL and DSC were concordant or discordant regarding the presence of hypoperfusion; we presented the data in terms of percentage agreement.

**TABLE 2** Stroke characteristics of subjects

| | Classification | Stroke characteristics |
|---|---|---|
| Lee et al.[14] | Vascular territory | 19 MCA, 3 PCA, 4 PICA<br>Multiple territory –<br>3 Watershed, 1 ACA + MCA, 1 MCA + PCA, 1 PICA + PCA |
| Zhang et al.[12] | Infarct territory | 14 Gray matter<br>16 Basal ganglia or centrum semiovale |
| Wolf et al.[4] | Etiology | 17 Large vessel occlusion, 10 Cardioembolic, 2 Other (ICA dissection), 7 Undetermined |
| Mirasol et al.[15] | Vascular territory | 20 MCA, 3 PCA, 1 Anterior choroidal |
| Bivard et al.[16] | Vascular territory | 9 ACA, 41 MCA, 8 ICA |
| Nael et al.[20] | Vascular territory and etiology | Large vessel occlusion –<br>9 Carotid, 28 MCA<br>4 Carotid dissection |
| Niibo et al.[17] | Vascular territory | 4 ICA, 19 MCA |
| Huang et al.[18] | Vascular territory | 39 ACA or MCA |
| Wang et al.[19] | Vascular territory | 24 MCA |
| Nael et al.[21] | Vascular territory and etiology | Large vessel occlusion –<br>6 Carotid, 15 MCA<br>4 Carotid dissection |
| Zaharchuk et al.[5] | Etiology | 26 Large artery steno-occlusive disease<br>17 Others |
| Bivard et al.[9] | Not reported | Not reported |
| Bokkers et al.[10] | Not reported | Not reported |
| Wang et al.[11] | Vascular and infarct territory | Vascular territory –<br>17 MCA<br>1 ACA + MCA<br>Infarct territory –<br>1 Cortical parietal lobe, 2 Basal ganglia, 2 Multiple infarcts, 3 Cerebellum and/or midbrain |
| Huck et al.[6] | Vascular and infarct territory | 5 MCA, 4 PCA, 1 PICA<br>5 Lacunar |
| Hernandez et al.[22] | Not reported | Not reported |
| Siewert et al.[13] | Vascular territory | 16 MCA, 1 PCA<br>1 Watershed (MCA + PCA) |

*Note*: This table shows the stroke characteristics of the subjects in this systematic review.
Abbreviations: ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery.

## Image quality

Eight of 17 studies assessed image quality of the scans obtained.[4,6,10,11,14,15,21,22] Six of these eight studies indicated that ASL and DSC image quality were of comparable quality based on ratings by observers.[4,10,11,14,15,22] Among these six studies, Wang et al. reported that image quality became significantly higher for both ASL and DSC when using a magnetic field strength of 3 Tesla (T) compared to 1.5 T.[11] Nael et al. and Huck et al. were the two studies that reported ASL's image quality as inferior to DSC's.[6,21] Contrary to Wang et al., Nael et al. reported that a change in magnetic field strength from 1.5 T to 3 T did not result in any statistically significant change in image quality for either ASL or DSC.[21]

## Correlation of ASL with DSC

Twelve of the 17 studies compared ASL and DSC to characterize the severity or extent of hypoperfusion areas[4,6,9–12,14,17–21] (Table 1). Correlation coefficient values ranged from 0.489[4] to 0.992[6] (Table 1). The majority of studies reported correlation that was ranked "moderate" to "very high," with the exception of Wolf et al.,[4] where the correlation of ASL with DSC for detection of hypoperfusion severity was ranked "low" (Table 1). Three studies used Wilcoxon signed rank test and/or *t*-test for a direct comparison of ASL with DSC for detection of hypoperfusion and found the two techniques not significantly different[13,21,22] (Table 1).

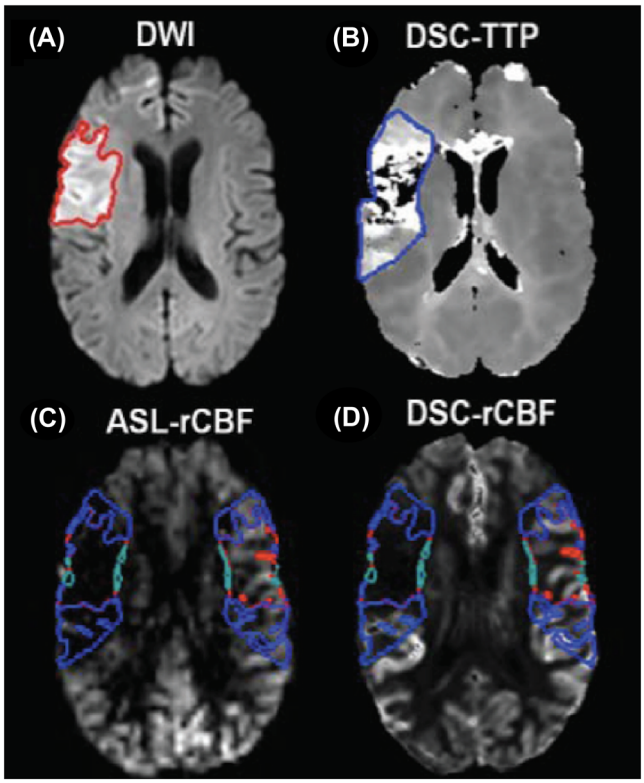


**FIGURE 2** Figure from Hernandez et al.'s paper.[22] Arterial spin labeling and dynamic susceptibility imaging detecting hypoperfusion with relative cerebral blood flow and time to peak. (A) Diffusion-weight imaging detecting infarct core. (B) Acute perfusion deficits using dynamic susceptibility contrast time to peak. (C and D) Infarct core is in green, mismatch in blue. Regions of interest also flipped to contralateral hemisphere to identify a region of healthy tissue as control. Abbreviations: DWI, diffusion-weighted imaging; rCBF, relative cerebral blood flow; TTP, time to peak

Seven studies compared ASL with DSC for detection of diffusion–perfusion mismatch either as correlation of the mismatch ratio or as percentage agreement of ASL with DSC regarding the presence or absence of mismatch[5,6,10,16,17,20,22] (Table 1). In one study, percentage agreement was 57%, judged "nondiscriminant,"[5] while for three studies, the percentage agreement ranged from 80% to 100%,[6,10,17] rated as "excellent" to "outstanding" (Table 1). Nael et al.'s correlation of the ASL mismatch ratio with that of DSC was ranked "very high" (*Pearson's correlation coefficient* ($r$) = 0.95),[20] while Bivard et al.'s findings were ranked "strong" (*Coefficient of determination* ($r^2$) = 0.73)[16] (Table 1).

Nael et al.'s 2012 study found that DSC demonstrated higher *relative cerebral blood flow* compared to ASL in hypoperfused areas after recanalization, while prior to reperfusion, *t*-test showed that ASL and DSC's findings were comparable[21] (Table 1). This suggests that ASL may underperform in the setting of small perfusion abnormalities. Additionally, anatomical location appears to be an important feature to consider. Zhang et al. found that ASL and DSC were most strongly correlated in cortical areas, compared to deep white matter.[12] Bivard et al. noted that ASL underestimated CBF in hypoperfused white matter.[16] Similarly, Huang et al. concluded that ASL signal may be less robust than DSC for assessment of white matter.[18]

The 17 studies included in this review employed different DSC perfusion parameters and none were designed to determine the optimal perfusion parameter for clinical use. For instance, some studies reported DSC CBF and MTT,[12] others reported DSC $T_{max}$,[5] or DSC TTP and CBF.[6] Three of the 17 studies did use a parametric design to assess perfusion parameter thresholds for the parameter studied.[16–18] For instance, Bivard et al. noted that an ASL CBF threshold of < 40% (compared to the contralateral region) and DSC $T_{max}$>6 s showed the highest area under the curve values for detection of ischemic penumbra, and that the mismatch lesion volumes derived from these two thresholds showed excellent correspondence with $r^2$ = 0.73.[16] Niibo et al. compared ASL CBF <15, 20, and 25 ml/100 g/min against DSC MTT >10 s, and found that ASL CBF < 20 ml/100 g/min had the highest correlation with DSC MTT > 10 s when estimating volume of hypoperfusion, with $r$ = 0.97.[17] Huang et al., on the other hand, compared DSC $T_{max}$ > 4, 5, and 6 s against ASL CBF, and found that ASL CBF had the highest correlation with DSC $T_{max}$ > 5 s when estimating volume of hypoperfusion, with $r$ = 0.82.[18] With only three articles addressing the issue of threshold, each using varying methods and studying different perfusion parameters, the results are too scant and lacking in consistency to support a consensus on optimal thresholds or perfusion parameter choice.

## Clinical endpoints

Three of the 17 studies reported on clinical endpoints. Bivard et al. reported in 2014 that an ASL CBF threshold of < 40% (compared to the contralateral region) and DSC $T_{max}$>6 s were the most accurate predictors of DWI lesions at 24 h.[16] Huang et al. reported that thresholds based on both DSC $T_{max}$>5 and >6 s provided the estimate of mean infarct volume close to final infarct size,[18] but that the mean infarct volume as estimated by ASL was significantly larger than estimated by DSC for both $T_{max}$ thresholds.[18] Bivard et al. reported in 2013 that hyperperfusion detected by ASL or reperfusion detected by DSC was useful information for identifying greater penumbral salvage as well as better 3-month clinical recovery, with ASL performing slightly better.[9] They noted, however, that only ASL hyperperfusion was associated with early clinical improvement.[9]

## Bias

We identified the following potential sources of bias: (1) Eight out of 17 studies had sample sizes fewer than 30 patients.[6,11,13,15,17,19,21,22] (2) Only eight out of 17 studies reported whether image quality was assessed.[4,6,10,11,14,15,21,22] (3) Nine out of 17 studies reported whether inter-rater reliability was assessed.[5,6,10,11,14,15,17,18,21] In terms of publication bias and the potential for missing information, our systematic search retrieved abstracts for which articles have not been published (e.g., conference proceedings), ongoing-studies, and two studies *whose*

*titles met inclusion criteria but had main texts written in foreign languages and were thus unable to be assessed.*[23,24] These findings, in addition to the likelihood that negative studies, in general, are less likely to be published, highlight the potential for missing information.

## DISCUSSION

Our systematic review found overall consistency, including moderate to very high correlation of ASL assessment of ischemic penumbra with that defined with DSC, no significant group difference between the two methods' assessments, and good agreement for studies that assessed hypoperfusion or mismatch status. The consistency of findings across these studies, which varied in the specific approaches to perfusion measurement, provides a degree of preliminary support for a role of ASL in the assessment of acute ischemic stroke, though it is important to keep the risks of bias and limitations of the studies in mind.

Low signal-to-noise (SNR) is a known limitation of ASL, which is most relevant to regions with inherently low perfusion. Thus, two studies noted that the consistency of ASL with DSC was superior in the cortex, compared to white matter.[12,18] ASL is also known to be sensitive to varying transit times across patients and brain regions,[11,12] and may have a tendency to overestimate the size of abnormal perfusions.[5,18] Newer techniques, such as velocity-selective ASL, which is an arterial delay-insensitive technique, and long-delay ASL, have been suggested to address transit times sensitivity in patients with cerebrovascular disease.[25,26] Techniques that use background suppression, such as multi-TI acquisitions, may also improve SNR.[16]

The finding of discrepancies between ASL and DSC was interpreted in some reports as evidence of a deficiency of ASL. Although DSC has been more extensively reported over a longer time compared to ASL, it nonetheless remains unclear whether DSC is truly a gold standard, since DSC measurements also face important limitations. Moreover, few studies assessed ASL and DSC for prediction of clinical outcome. Clinical studies are needed to assess ASL and DSC in the management of stroke patients with respect to relevant clinical outcomes, in particular because ASL could benefit certain patients for whom gadolinium contrast may be contraindicated.[27]

A limitation of the papers we identified for this review is the heterogeneity of perfusion parameters studied, particularly for DSC. An important unresolved question is which hemodynamic parameters derived from DSC are most useful and reliable for the assessment of stroke. This point is beyond the scope of our review, which is inherently limited to the parameters reported by the studies that we included. Notably, no consensus exists regarding which parameter or combination of parameters is optimal for DSC,[6] though it is known that the optimal perfusion parameter is time dependent when it comes to detecting ischemia,[28] because the perfusion abnormalities in ischemic areas of the brain become more abnormal with greater intervals from onset to imaging.[28] Only three studies in our review attempted to determine optimal perfusion parameters for detecting tissue at risk, and each used varying methods with different outcomes of interest.[16–18] For instance, Niibo et al. compared several ASL perfusion lesion thresholds against a single DSC perfusion lesion threshold,[17] while Huang et al. did the opposite and compared several DSC thresholds against a single ASL threshold.[18] The remaining studies compared ASL and DSC with data available to them, but optimal perfusion parameters and optimal timed thresholds were not an outcome of interest; in fact, several studies reported perfusion parameter but did not report timed thresholds. Thus, the results are too scant and lacking in consistency to support a consensus on optimal perfusion parameters.

Some additional limitations include several studies of small sample, fewer than 30 patients,[6,11,13,15,17,19,21,22] as well as the lack of important supplementary findings, such as assessment of image quality and inter-rater reliability in a few studies, as noted in the Results section. And finally, the studies of this systematic review focused more on anterior circulation strokes and strokes affecting cortical gray matter, anatomical locations where ASL may be more accurate, thus increasing the risk of bias.

In assessing the results of our review and their potential real-world implications for clinical practice, it is important to consider several practical issues related to implementation and utilization. MR perfusion imaging in general requires careful implementation and postacquisition analysis, for which expertise may not be widely available outside of large academic centers.[29] ASL is newer to the clinic compared to DSC and thus may be less widely available. Base configurations of current MR scanners will generally include capability for DSC but may or may not include ASL without additional software purchase, which could be as high as USD 30,000–100,000. Advantages of DSC include shorter time to acquire (~1 min) and ability to cover the entire brain at higher resolution (e.g., 2 mm).[30] ASL, even at 3T, suffers from low SNR, requiring coarser resolution (3–4 mm) and longer acquisition time (4 min or longer).[31] Perhaps, partially balancing the longer ASL acquisition is the fact that administration of contrast is obviated, saving cost, time, and risk. Both methods require postacquisition processing of images. This may be available in-line, yielding immediately viewable perfusion maps, or require offline processing. Achievement of truly quantitative CBF measurement is more robust with ASL compared to DSC, whereas DSC can provide measures of CBV not available from ASL.[29] Anticipated improvements, including methods that leverage machine learning, in postacquisition processing could expand clinical utility based upon improved speed and reliability.

Acute stroke triage revolves around maximally expedited revascularization. In this context, CT has assumed a preeminent role based on its ability to provide the anatomic and hemodynamic data needed for decision making in a very short timeframe.[32,33] Notwithstanding, the ability of diffusion MR to more specifically define the infarct core and, thereby, its penumbra,[29,34] it remains unclear whether MRI-based triage would ever supplant CT outside of very specialized centers. The largest obstacle in acute triage cases is likely to be the time involved in MR screening, safety, and setup, not simply acquisition time. However, perfusion MR also has many benefits; it is far more sensitive, provides higher quality imaging, and is far less error prone;[29,34] hence, efforts have been made to improve the suitability of this technique for acute ischemic stroke intervention. Since one of the major disadvantages of

perfusion MR imaging is time consumption, comprehensive MR protocols have been studied in several clinical trials in order to improve acquisition speed; Nael et al.'s paper describes a successful trial of a 6-min magnetic resonance imaging protocol.[33]

Other stroke applications may also benefit from the added information provided by MR perfusion and diffusion measurements. For example, when selecting for endovascular thrombectomy in the case of large vessel occlusion stroke and for late window thrombolysis, CT perfusion imaging or a combination of diffusion and perfusion MR imaging can be used. Studies have also shown that perfusion MR imaging enables the identification of patients with treatment targets that are beyond the conventional time windows for endovascular thrombectomy or intravenous thrombolysis treatment.[34] As another example, patients presenting late after onset may benefit more than those in the hyperacute phase, if MR perfusion can be shown to more reliably determine the risk of intervention.[32] In complex cases or children, MR is valuable because of its ability to allow for repeated perfusion measures while avoiding radiation exposure; ASL in particular is useful because it avoids chemical contrast and is entirely noninvasive.[34]

In conclusion, the extant literature provides *a degree of preliminary indication* that ASL can delineate cerebral perfusion deficits in acute ischemic stroke similar to DSC. Considering the wide variation in terms of data acquisition techniques, perfusion parameters utilized, and statistical approach, *along with the risk of bias in a few studies in this review*, future research would benefit from standardization of research methods, to facilitate more robust conclusions across studies. Additionally, further research addressing clinical relevance and endpoints in larger numbers of patients is warranted to definitively determine the utility of noncontrast ASL in the clinical assessment of acute ischemic stroke.

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None.

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