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REVIEW

The utility of apparent diffusion coefficients for predicting treatment response to uterine arterial embolization for uterine leiomyomas: a systematic review and meta-analysis

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PURPOSE
Apparent diffusion coefficient (ADC) values, which are derived from diffusion-weighted imaging, have a potential role for predicting treatment response. A systematic review was conducted to examine the value of baseline ADC values for predicting leiomyoma size reduction after uterine arterial embolization (UAE).

METHODS
Study selection, quality appraisal and data extraction were conducted independently by two authors. Statistical analyses included the calculation of weighted means and summary correlation coefficients (under the random effects model).

RESULTS
Eleven studies consisting of a total of 258 patients (age, weighted mean±standard deviation [SD], 43.1±10.1 years) were included. The weighted mean±SD ADC value was 1.2±1.5 $\times 10^{-3}$ s/mm^2 at baseline (ten studies) and 1.3±2.8 $\times 10^{-3}$ s/mm^2 at approximately 6 months after embolization (six studies). The weighted mean percentage leiomyoma volume reduction (VR) at 6 months was 47.1%±35.6% (seven studies). Based on four studies, the weighted summary correlation coefficient for the correlation between baseline ADC and leiomyoma VR at approximately 6 months was not significant (r=0.40; 95% CI, -0.07 to 0.72; I^2=69.7%). No associations were found in three of the four studies that examined changes in ADC values as a predictor.

CONCLUSION
Due to high heterogeneity, it is unclear whether ADC may be useful for predicting treatment responses to UAE.

A common benign tumor of the female pelvis is uterine leiomyoma (1). Uterine leiomyomas causing bulk-related pain, menorrhagia, or other symptoms are indications for treatment (2). One of the most widely used and effective treatments for uterine leiomyoma is uterine artery embolization (UAE) (3). The goal of uterine artery embolization is to permanently occlude the uterine arterial branches supplying the leiomyomas, eventually leading to their devascularization and infarction (4). However, recurrence or residual leiomyomas may require further interventions with re-embolization or surgical procedures. Predicting the response of uterine leiomyoma to embolization may be helpful for appropriately selecting patients for embolization and for the early evaluation of response to treatment.

The interest to use functional imaging techniques such as diffusion-weighted magnetic resonance imaging (DWI) to monitor and predict treatment outcomes has emerged during the past years (5). DWI is a noninvasive imaging modality that does not require the administration of contrast agents (6). DWI visualizes tissue characteristics by assessing the Brownian (random) motion of water molecules (7, 8). The diffusion motion of water molecules is affected by a variety of factors, such as cellular membrane integrity, extracellular fluid viscosity, cellularity, and tissue vascularity (9). DWI can provide quantitative information on tissue characteristics through a value known as the apparent diffusion coefficient (ADC) calculation (7, 8). Both ADC and DWI have been adopted in many fields, including oncology and neurology (10–12).

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There is growing interest to use of ADC as a noninvasive imaging biomarker for monitoring tissue changes and predicting leiomyoma response to UAE over the past years. The primary objective of this systematic review was, therefore, to examine whether baseline ADC values could predict leiomyoma size reduction (i.e., volume reduction [VR] in patients undergoing UAE for symptomatic uterine leiomyomas). The secondary objectives were to examine whether changes in ADC (from baseline to post-embolization) could predict leiomyoma VR.

Methods

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (13).

Search strategy

An electronic search was initially conducted in the following databases in late November 2015: MEDLINE and MEDLINE In-process & Other Non-Index Citations, EMBASE, Cochrane Central Register of Controlled Trials and PubMed. Updated searches were conducted until January 2018. The search terms, which were combined using Boolean operators ("or" and "and"), included the following: uterine leiomyomas, leiomyoma, myoma, fibroma, fibromyoma, fibroleiomyoma, leiomyomata, uterine artery embolization, apparent diffusion coefficient, diffusion-weighted magnetic resonance imaging, and diffusion-weighted imaging. Medical subject headings, alternatives and variations of the terms were also used. No date restrictions were placed on the database searches.

Study selection and eligibility criteria

Two reviewers screened the titles and abstracts of the search results to identify potentially relevant studies. The same two reviewers then independently applied the eligibility criteria to the full-text of the studies that passed the title/abstract screening. Studies were included if they met the following criteria: 1) prognostic studies with observational (retrospective or prospective) or randomized research design, 2) evaluating ADC as a predictor factor for post-UAE change in uterine leiomyoma volume, diameter or size (at any follow-up time point), and 3) included women receiving UAE for the treatment of uterine leiomyomas. Case reports, case series, grey literature, conference abstracts, and review papers were excluded. Studies involving repeat embolization were also excluded.

Main points

- Considering the variability and inconsistency in the current literature, it is currently unclear whether ADC may be useful for predicting treatment responses to UAE.
- Standardization of ADC calculation and interpretation approaches for uterine leiomyomas is needed.
- Future studies should incorporate patient important outcomes such as symptom relief.

Methodologic quality assessment

Two reviewers independently assessed the validity and risk of bias of the included studies based on the domains used in the Risk of Bias Assessment Instrument for Prognostic Factor Studies (QUIPS) tool (14). The tool assesses the possibility of bias in the following domains: study participation (the possibility that the relationship between ADC values and the outcome is different between study participants and eligible non-participants), study attrition (the possibility that the relationship between ADC values and the outcome is different between participants who completed the study and participants who were lost to follow-up), measurement of prognostic factors (the possibility that the measurement of ADC values are different between participants and outcome levels), outcome measurement (examines whether methods for outcome measurement were valid and reliable, and the possibility of the measurements may be affected by ADC findings, i.e., due to lack of blinding), study confounding (whether important confounders were accounted for), and statistical analysis and reporting (the likelihood of the results being spurious or biased due to the analysis or reporting).

Statistical analysis

Data for the analysis was extracted from each individual study by two reviewers using a standardized spreadsheet. The level of agreement between the two reviewers with respect to the study selection was measured using the Kappa statistics with corresponding confidence intervals (CI).

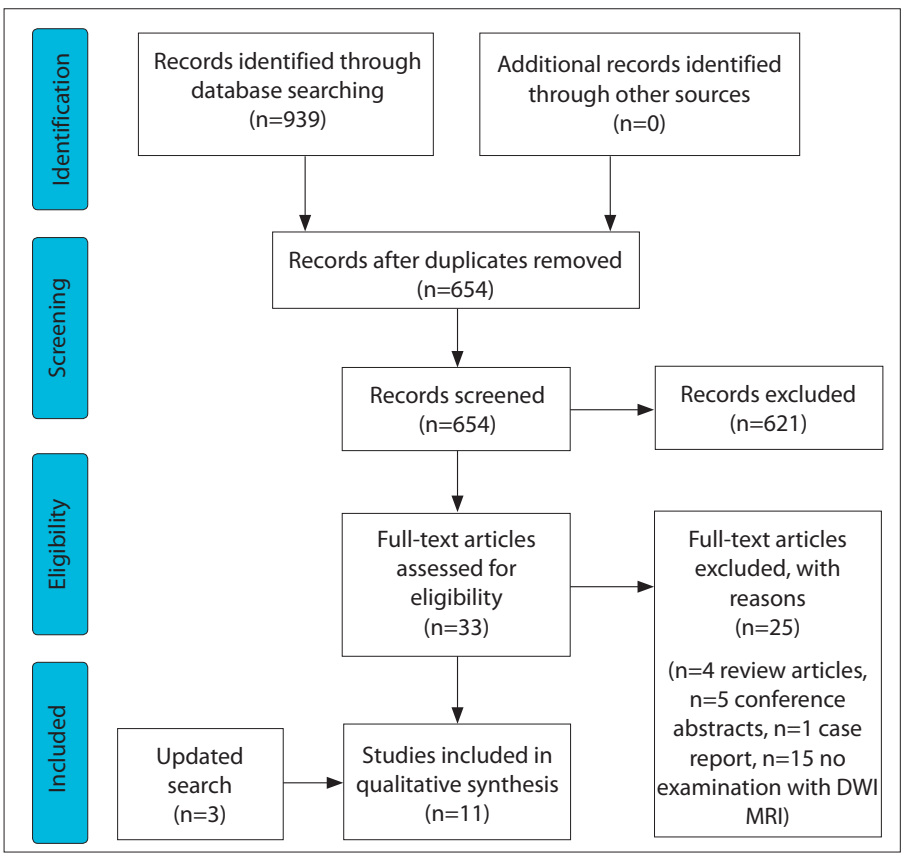

Figure 1. PRISMA flow diagram. The figure shows the study identification, screening and selection process, which was done independently by two reviewers.

Table 1. Summary of included studies

First author, year	Study design	Location	Time frame	Follow-up period	Sample size	Mean age (range), years
Ananthakrishnan, 2012 (18)	Retrospective	United Kingdom	2011	6 months	15 patients	40 (33–52)
Bao, 2017 (28)	Retrospective	United States	May 2009 to July 2014	6 months (mean 7.4)	18 patients (59 fibroids)	46 (40–53)
Cao, 2014 (19)	Prospective	China	Nov 2011 to May 2013	6 months	11 patients (16 fibroids)	42 (29–56)
Cao, 2017 (27)	Retrospective	China	Feb 2012 to Dec 2013	6 months	12 patients (17 fibroids)	Median: 42 (24–56)
Faye, 2013 (20)	Retrospective	France	July 2007 to March 2009	6 months	17 patients (27 fibroids)	45 (38–58)
Hecht, 2011 (21)	Retrospective	United States	Dec 2006 to April 2009	Mean 6.8 months	11 patients (28 fibroids)	43 (NR)
Kirpalani, 2014 (22)	Retrospective	Canada	Sep 2009 to March 2011	6 months	50 patients (88 fibroids)	45 (26–55)
Lee, 2013 (23)	Prospective	South Korea	May 2011 to Jan 2012	3 months	49 patients (72 fibroids)	41 (29–55)
Liapi, 2005 (24)	Retrospective	United States	April 2002 to March 2003	Mean 6.0 months	11 patients (32 fibroids)	41 (32–51)
Noda, 2015 (25)	Retrospective	Japan	May 2007 to April 2013	Mean 2.9 months	15 patients (52 fibroids)	46 (36–53)
Sutter, 2016 (26)	Retrospective	France	Aug 2008 to June 2012	6 months	49 patients	41 (35–54)

NR, not reported.

Weighted means and standard deviations (SD) were calculated based on each study's unit of analysis (number of patients or leiomyomas). For studies that did not report the weighted mean for an entire cohort, averages from the study's subgroups were used. For studies with unit of analysis (number of patients or leiomyomas) greater than 25 that did not report mean values, median values were used instead (15). For studies with smaller unit of analysis that did not report mean values, the formula suggested by Hozo et al. (15) was used to estimate the mean. The MedCalc Software 17.9 (MedCalc) was used to conduct the meta-analysis of correlation coefficients under the fixed and random effects model (using the Hedges-Olkin method, and the DerSimonian and Laird model, respectively) (16, 17). All other statistical analyses were performed using JMP Pro 13 (SAS Institute) and Statistical Package for Social Sciences, version 25.0 (IBM Corp.).

Results

A total of eleven studies were included in the systematic review (18–28). A flow diagram of the search and screening process can be seen in Fig. 1. The strength of agreement between the two reviewers on the selection of the final studies was considered "very good" (Kappa statistic=0.82; 95% CI, 0.58 to 1.00).

Eleven studies consisting of 258 patients (age, weighted mean±SD, 43.1±10.1 years) were included. A description of each of the studies can be found in Table 1. Only 7 of the 11 studies examined whether baseline ADC values could predict leiomyoma VR (18–23, 25). Only one of the 11 studies examined whether baseline ADC values could predict leiomyoma diameter reduction (28). Four studies examined whether changes in ADC (from baseline to 6-month follow-up) could predict 6-month VR (20, 22, 26, 27). No studies examined clinical outcomes such as symptom relief or recurrence rates. The risk of bias for the included prognostic studies on each domain was mostly rated as moderate to high (See Supplemental Table).

The methods used to determine ADC values varied among the 8 studies that used leiomyoma volume as an outcome measure (Table 2). Specifically, the *b* values (s/mm^2) used for the calculation of ADC and the image analysis protocol varied. Four studies (18, 21, 23, 26) indicated that two reviewers conducted the assessment independently while 7 studies (19, 20, 22, 24, 25, 27, 28) did not (i.e., used one assessor, assessed by consensus or no mention of assessment method). Two studies indicated that the assessor(s) were blinded to the clinical history and/or embolization outcomes of each patient (20, 23). Furthermore, the number of *b* values used also varied among the studies. Eight studies (18–21, 23–25, 27) used two *b* values while only two studies used more than two *b* values (22, 26). One study did not report the *b* values used (28).

The ADC values and leiomyoma size parameters at baseline and after embolization are demonstrated in Table 3. The weighted mean ADC value was 1.2±1.5 $\times 10^{-3}$ s/mm^2 at baseline based on 10 studies (18–27) and 1.3±2.8 $\times 10^{-3}$ s/mm^2 at approximately 6 months after embolization based on 6 studies (18, 20, 22, 24, 26, 27). The weighted mean percentage reduction in leiomyoma volume at 6 months was 47.1%±35.6% based on 7 studies (18–22, 26, 27).

Four studies (18, 19, 21, 23) showed a positive association or correlation between baseline ADC and leiomyoma VR (three at 6-month follow-up and one at 3-month follow-up) (Table 4).

Ananthakrishnan et al. (18) found a significant correlation between baseline ADC

Table 2. Uterine arterial embolization and MRI procedure details

First author, year	Embolization agent type & size	Embolization endpoint	MRI System	Fibroid(s) examined	ADC measurement	Volume calculation method	MRI assessment protocol
Ananthakrishnan, 2012 (18)	Polyvinyl alcohol particles; 500–700 μm (Cook Medical)	Complete stasis	1.5 T Signa HDxt (GE Medical Systems)	Dominant fibroid in each patient	Calculated using *b* values of 0 and 1000 s/mm^2)	Anteroposterior × craniocaudal × transverse long axis × 0.5233	Independently evaluated by two radiologists and an MRI physicist with consensus to resolve disagreements
Bao, 2017 (28)	Embospheres; 500–700 μm (Biosphere Medical)	Antegrade flow stasis	Not reported	Minimum fibroid size of 2 cm	Not reported	Diameter assessed only	Not reported
Cao, 2014 (19)	Nonspherical polyvinyl alcohol particles (Alicon Medical); 250–350 μm or 350–560 μm followed by 350–560 μm or 560–710 μm	Complete cessation of blood flow in ascending uterine artery during 10 cardiac beats	3.0 T HDxt system (GE Medical Systems)	One patient had 3 fibroids, 3 pts had 2 fibroids and remaining pts had 1 fibroid	Calculated using *b* values of 0 and 1000 s/mm^2	Length × width × height × 0.52 (on T2-weighted images); VR formula: (Baseline volume – PE volume)/Baseline volume × 100%	Assessed in consensus by two radiologists
Cao, 2017 (27)	Nonspherical polyvinyl alcohol particles mixed with 100 mL of 1:1 saline solution and contrast agent mixture (Alicon Medical); 250–560 μm	Uterine artery stasis	3.0 T HDxt system (GE Medical Systems)	Minimum fibroid size of 2 cm; 1–3 fibroids in each patient (if more than 3, largest ones were examined)	Calculated using *b* values of 0 and 1000 s/mm^2	VR formula: (Baseline volume – PE volume)/Baseline volume × 100%	Assessed in consensus by two radiologists
Faye, 2013 (20)	Calibrated trisacryl gelatin microspheres (Embosphere, Biosphere, Merit Medical); 500–700 μm	Stasis or near stasis	1.5 T system (HDxt; GE Medical Systems)	1–3 fibroids in each patient including dominant fibroid (mean 1.6 fibroid per patient)	Calculated using *b* values of 0 and 500 s/mm^2	Length × height × width × 0.5	Image analysis done by one reader blinded to patient history and clinical results
Hecht, 2011 (21)	Trisacyl gelatin microspheres (Biosphere Medical)	Cessation of blood flow in fibroids and ascending uterine artery without proximal reflux of contrast within the uterine artery	1.5 T MR scanners (Avanto, Sonata Vision or Symphony)	1–4 fibroids in each patient including dominant fibroid (≥2 in 8 pts)	Calculated using *b* values of 500 and 1000 s/mm^2	(Anterior–posterior × transverse × craniocaudal dimensions) × 0.5; or volumetric measurement (obtaining cross-sectional area of each lesion using the freehand ROI outlining tool); VR formula: (Baseline volume – PE volume)/Baseline volume × 100%	Independent assessment with two separate methods by two authors

Table 2. Uterine arterial embolization and MRI procedure details (cont'd)

First author, year	Embolization agent type & size	Embolization endpoint	MRI System	Fibroid(s) examined	ADC measurement	Volume calculation method	MRI assessment protocol
Kirpalani, 2014 (22)	Polyvinyl alcohol particles (Contour-SE, Boston Scientific); 355–500 µm	Stasis in both uterine arteries	1.5 T system (Achieva, Phillips Medical Systems)	Largest (dominant) fibroid or the 2 largest fibroids if more than 1 fibroid identified (>2 fibroids in 34 pts, 2 fibroids in 4 pts, and 1 fibroid in 12 pts)	Calculated using *b* values of 0, 250, 500 and 750 mm^2/s	Length × width × height × 0.5236; VR formula: (Baseline volume – PE volume)/Baseline volume × 100%	Fibroid analysis was performed by one fellowship-trained radiologist with 2 years of experience in pelvic MRI
Lee, 2013 (23)	Nonspherical polyvinyl alcohol particles (Contour, Boston Scientific); followed by gelatin sponge particles if ovarian artery collateral supply fibroids (Gelastypt, B. Braun Melsungen)	Complete cessation of blood flow in the ascending and transverse segments of the uterine artery for 10 cardiac beats	3.0 T system (HDxt; GE Medical Systems)	All fibroids ≥3 cm	Calculated using *b* values of 0 and 1000 s/mm^2	Length × width × height × 0.5; VR formula: (Baseline volume – PE volume)/Baseline volume × 100%	Assessed independently by two radiologists blinded to embolization outcomes
Liapi, 2005 (24)	Tris-acryl gelatin microspheres (Embosphere, Biosphere Medical); 500–900 µm	--	1.5 T system (CV/i, GE Medical Systems)	All fibroids ≥2 cm	Calculated using *b* values of 0 and 500 s/mm^2	--	Two experienced radiologists performed the image analysis in consensus
Noda, 2015 (25)	Gelatin sponge particles (350 mg/mL)	Adequate occlusion of the bilateral, proximal ascending uterine artery	1.5T system (Achieva, Philips Medical Systems)	All fibroids	Calculated using *b* values of 0 and 1000 s/mm^2	Length × width × height × 0.5233; VR formula: (Baseline volume – PE volume)/Baseline volume; Affected fibroids (PE VR rate > median of all fibroid) vs. unaffected fibroids PE VR rate < median of all fibroid)	Two radiologists performed the image analysis in consensus
Sutter, 2016 (26)	Trisacryl microspheres (Embosphere, Biosphere Medical); 500–700 µm and 700–900 µm	Stasis or near stasis in the ascending segment of uterine artery	1.5 T system (Magnetom Avanto, Siemens Healthcare)	Dominant fibroid	Calculated using *b* value of 0, 500 and 1000 s/mm^2	Length × width × height × 0.52; or semi-automatic segmentation method (with contrast-enhanced 3D VIBE MR images)	Assessed independently by two radiologists

MRI, magnetic resonance imaging; ADC, apparent diffusion coefficient; Pts, patients; PE, postembolization; VR, volume reduction.

and 6-month percentage VR of the dominant leiomyoma (r=0.66, $P = 0.007$). Cao et al. (19) also found a significant correlation between ADC and 6-month VR (r=0.61, $P = 0.012$). Hecht et al. (21) on the other hand found a moderate correlation between baseline ADC and VR at a mean follow-up of 6.8 months (r=0.41, $P = 0.017$). At 3-month follow-up, Lee et al. (23) found that baseline ADC was associated with leiomyoma volumetric response ($P = 0.014$). In contrast, three studies did not show that baseline ADC was associated or correlated with leiomyoma VR (20, 22, 25). Faye et al. (20) found no significant differences in baseline

Table 3. ADC values and uterine fibroid volume

First author, year	ADC values					
	Baseline ($\times 10^{-3}$ mm^2/s)	PE ($\times 10^{-3}$ mm^2/s)	Baseline vs. PE	Baseline fibroid volume (cm^3)	PE fibroid volume (cm^3)	Volume reduction (%)
Ananthakrishnan, 2012 (18)	Mean±SD: 1.01±0.39	6-mo mean±SD: 0.48±0.26	$P < 0.001$	Mean±SD: 263±170	6-mo mean±SD: 130±107	6-mo: 51%
Bao, 2017 (28)	Mean±SD: 708.5±74.2	–	–	Mean±SD diameter: 53.6±3.9	Mean±SD diameter: 44.0±3.7	Mean diameter reduction: 20%
Cao, 2014 (19)	Mean (range): 1.37 (1.05–2.32)	–	–	Mean (range): 72.6 (7.3–347.1)	6-mo mean (range): 34.6 (1.5–174.8)	6-mo mean: 58.9%
Cao, 2017 (27)	Median (range): 1.20 (0.86–1.66)	6-mo median (range): 1.56 (1.00–1.86)	$P = 0.0003$	Median (range): 67.9 (7.3–657.9)	6-mo median (range): 21.5 (1–223.7)	6-mo median: 54.8%
Faye, 2013 (20)	Median (IQR): 1.61 (1.40–1.80)	1-w median (IQR): 1.53 (1.40–1.60); 6-mo median (IQR): 1.27 (1.10–1.50)	1-w $P = 0.13$; 6-mo $P = 0.002$	Median (IQR): 79 (37–164)	1-w median (IQR): 70 (34–171); 6-mo median (IQR): 32 (13–103)	1-w median: 11% 6-mo median: 54%
Hecht, 2011 (21)	Mean (range): 0.80 (0.37–1.71)	–	–	Median (range): 47 (18–182)	–	Mean at 6.8 mo: 48%
Kirpalani, 2014 (22)	Mean±SD: 1.30±0.20	6-mo mean±SD 1.68 (0.24)	$P < 0.0001$	Mean±SD: 167.7±228.6*; Median (range): 65.6 (0.5–1331.6)*	6-mo mean±SD: 97.5±160.4*; 6-mo median (range): 34.1 (0.2–1070.1)*	6-mo mean±SD: 43.7%±24.2%
Lee, 2013 (23)	Mean (range): 1.17 (0.559–1.814)	–	–	Median (range): 65.1 (8.5–661.2)	–	3-mo mean±SD: 44.1%±18.4% (27 fibroids showed ≥50% VR, 45 showed <50% VR)
Liapi, 2005 (24)	Mean (range): 1.74 (1.23–2.10)	6-mo mean (range): 1.22 (0.14–3.30)	$P < 0.01$	–	–	–
Noda, 2015 (25)	Mean (range) Affected fibroids: 1.11 (0.66–1.62); Unaffected fibroids: 1.18 (0.57–3.75)	–	–	Mean (range) Affected fibroids: 83.2 (0.7–842.4); Unaffected fibroids: 72.8 (0.7–360.4)	Mean (range) at 2.9 mo Affected fibroids: 34.8 (0.3–318.9); Unaffected fibroids: 58.6 (0.6–284.5)	Mean±SD at 2.9 mo Affected fibroids: 56.5%±14.4%; Unaffected fibroids: 19.4%±18.7%
Sutter, 2016 (26)	Mean±SD Reader 1: 1.096±0.212; Reader 2: 1.113±0.241	6-mo Mean±SD Reader 1: 0.712±0.375; Reader 2: 0.751±0.389	$P < 0.001$	Mean±SD Reader 1: 177±291; Reader 2: 180±300	6-mo mean±SD Reader 1: 110±216; Reader 2: 113±219	6-mo mean±SD: 41%±26%

ADC, apparent diffusion coefficient; PE, postembolization; SD, standard deviation; mo, month(s); w, week; IQR, interquartile range; VR, volume reduction.
*Reported as mL.

ADC between leiomyomas with VR greater than 50% versus less than 50% at 6-month follow-up ($P = 0.07$). The study by Kirpalani et al. (22) which used four *b* values in their ADC calculations, found no significant correlation between the baseline ADC and 6-month percent volume change (r=-0.06, $P = 0.5485$). Lastly, Noda et al. (25) found that there were no differences in baseline ADC values between affected leiomyomas (VR rate at postembolization greater than the median of all leiomyomas) and unaffected (VR rate at postembolization less than the median of all leiomyomas) at approximately 3 months postembolization ($P = 0.510$). One recent study by Bao et al. (28) found that baseline ADC values were associated with percent change in fibroid diameter.

Three studies conducted a receiving operating curve (ROC) analysis to determine whether baseline ADC could predict >50% or ≥50% VR (19, 21, 23). Hecht et al. (21) demonstrated that baseline ADC could predict >50% VR at an optimal cutoff value of 0.873 $\times 10^{-3}$ mm^2/s (sensitivity, 70%; specificity, 83%). Meanwhile, Lee et al. (23) found that the optimal cutoff value of baseline ADC for predicting ≥ 50% VR was 1.092 $\times 10^{-3}$ mm^2/s (AUC, 0.699; sensitivity, 82.6%; specificity, 52.3%). However, the study conducted by Cao et al. (19) found that the combination of baseline ADC and entropy values from T2-weighted imaging (entropy values are associated with tissue heterogeneity) was the most accurate model for predicting ≥50% VR than models with ADC or entropy alone.

A meta-analysis of four studies that reported correlation coefficients between baseline ADC and leiomyoma VR at approximately 6 months is shown in Fig. 2 (18, 19, 21, 22). The meta-analysis, consisting of a total of 87 patients, did not demonstrate a significant correlation between baseline ADC values and leiomyoma VR under the random effects model (weighted summary correlation coefficient, 0.40; 95% CI, -0.07 to 0.72). It is also important to note

Table 4. Relationship between ADC and fibroid size

First author, year	Baseline ADC	Change in ADC
Ananthakrishnan, 2012 (18)	Significant, positive correlation between baseline ADC and 6-month VR (r=0.66, *P* = 0.007)	--
Bao, 2017 (28)	Baseline ADC was associated with percent change in fibroid diameter (*P* = 0.04)	--
Cao, 2014 (19)	Significant, positive correlation between baseline ADC and 6-month VR (r=0.61, *P* = 0.012)	--
Cao, 2017 (27)	--	Significant correlation between change in ADC and 6-month VR (ρ= -0.5, *P* = 0.04)
Faye, 2013 (20)	No significant differences in baseline ADC values between fibroids with 6-month VR >50% vs. <50% (*P* = 0.07)	No significant correlation between change in ADC and 6-month VR (r= -0.07, *P* = 0.72)
Hecht, 2011 (21)	Significant, positive correlation between baseline ADC and VR (at mean 6.8 month) (ellipsoid formula approach: r=0.49, *P* = 0.029; volumetric measurement approach: r=0.41, *P* = 0.017)	--
Kirpalani, 2014 (22)	No significant correlation between baseline ADC and 6-month VR (r= -0.06; *P* = 0.5485)	No significant correlation between change in ADC and 6-month VR (r= -0.06; *P* = 0.5485)
Lee, 2013 (23)	Significant association between baseline ADC and 3-month VR (*P* = 0.014); High ADC associated with greater VR	--
Liapi, 2005 (24)	--	--
Noda, 2015 (25)	No significant difference in baseline ADC values between affected fibroids (PE VR rate > median of all fibroid) and unaffected (PE VR rate less than median of all fibroids (*P* = 0.510)	--
Sutter, 2016 (26)	--	No correlation between change in ADC and 6-month VR (ρ=0.15, *P* = 0.31)

ADC, apparent diffusion coefficient; PE, postembolization; VR, volume reduction.

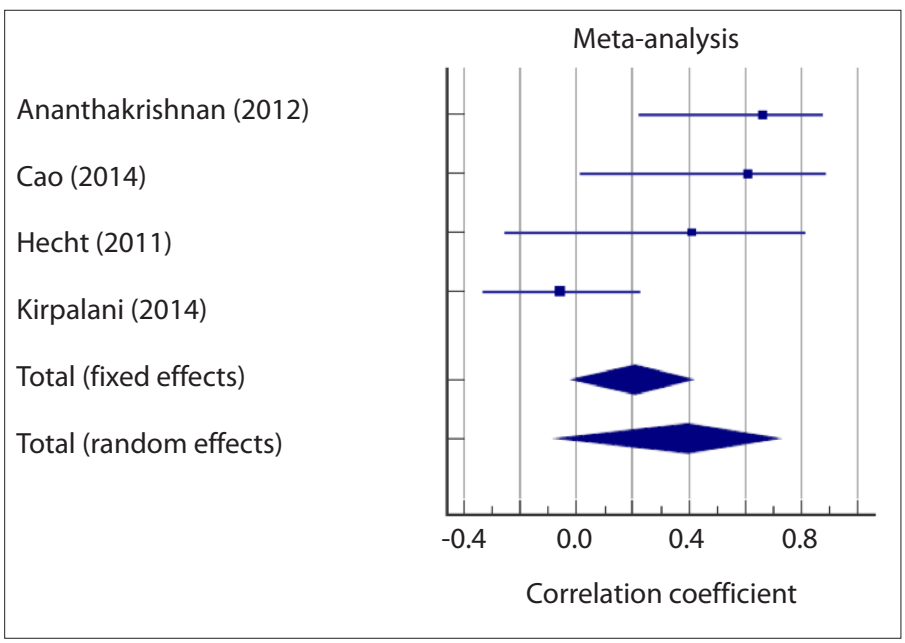

Figure 2. Meta-analysis of studies reporting the correlation between baseline ADC and fibroid volume reduction at approximately 6 months. Meta-analysis of four studies show that the weighted summary correlation coefficient was r=0.40 (95% CI, -0.07 to 0.72; *P* = 0.09) under the random effects model, and r=0.21 (95% CI, -0.01 to 0.41; *P* = 0.07) under the fixed effects model. Test for heterogeneity shows I^2=69.7% (*P* = 0.02).

that there is high heterogeneity among the studies included in the meta-analysis (I^2=69.7%, *P* = 0.02).

Three studies did not find any significant correlation between change in ADC values (from baseline) and VR at 6 months (Table 4) (20, 22, 26). However, one recent study based on 17 fibroid samples found a significant correlation (27). Due to high heterogeneity, no further meta-analyses were conducted on these four studies.

Discussion

The present systematic review and meta-analysis, which included 11 studies, examined the use of ADC for predicting outcomes after uterine arterial embolization. The meta-analysis, despite demonstrating high heterogeneity, showed that there is no correlation between baseline ADC values and leiomyoma VR at approximately 6 months (r=0.40; 95% CI, -0.07 to 0.72; I^2=69.7%). The results therefore indicate that the potential of both baseline and changes

in ADC (from baseline to postembolization) for predicting treatment response to UAE is currently unclear. The heterogeneity in the literature could be explained by a number of factors including variations in the following: technical factors (e.g., the radiologist' measurement definitions, MRI vendor or system used), the DWI assessment and sequencing methods used (e.g., selection of *b* values), biological characteristics of uterine leiomyomas, embolization agent size and type, and the embolization technique and endpoints used. The heterogeneity could also be explained by the included studies' methods ranging from sample size and patient selection.

The selection of *b* values for calculating ADC values significantly varied among the included studies. This is essential to consider since it has been known that the diffusion-weighted sequences must be appropriate for the tissue being examined (9). As a general rule of practice, DWI is usually performed with at least two *b* values. This consists of values at 0 s/mm^2 and 500–1000 s/mm^2. However, applying more than two *b* values could improve the accuracy of the ADC produced (9). Interestingly, two studies that used more than two *b* values did not find a correlation between ADC values and their examined endpoints (leiomyoma VR or degree of devascularization) (22, 26). Further investigations are therefore needed to confirm which *b* values are most ideal for assessing leiomyoma treatment response after UAE.

In addition to the diffusion sensitizing gradient chosen, the variation in ADC values among the included studies could also be due to the different DWI techniques used. DWI scanning parameters (local protocol, patient set-up, and skill level of the radiologist), MRI system or hardware used, and other factors have also been shown to cause variations in ADC values (9, 29). There are also several inherent limitations of DWI that could also explain the variability in results. One limitation is that the technical variance associated with certain parameters (aside from *b* values and geometry) cannot be replicated across different MRI system platforms. These parameters include DWI waveform design and echo-spacing (29). Other possible limitations of DWI include low signal-to-noise ratio (SNR) and increase likelihood of artifacts (9). Consensus on DWI and ADC calculation approaches for uterine leiomyoma are therefore needed.

The histopathologic characteristics of leiomyomas (e.g., cellularity) could contribute to the heterogeneity seen among the included studies (30). The diffusion of water in tissues is known to be affected by various cellular and tissue components (e.g., cell membrane integrity) and that a defect or decrease in tissue cellularity allows for greater water molecule movement (9). Cellular density and composition has also been shown to vary with uterine leiomyoma size (31). Histopathologic factors are therefore important to consider as it could affect variations in ADC values (which reflects diffusion motion of water molecules). Uterine leiomyomas are also known to be well-perfused and thus ADC values may also be a reflection of blood flow in the capillaries (i.e., perfusion) (32).

In addition to leiomyoma tissue characteristics, ADC values may also vary with different patient characteristics. One study found that the ADC values of normal uterine myometrium differed according to various menopausal and premenopausal (menstrual, proliferating and secretory) phases (33). Hence both histopathologic features of leiomyomas and patient characteristics may need to be considered when interpreting ADC values.

The methodologies used in the included studies varied significantly and possessed several limitations. A major limitation is that the majority of studies had very small sample sizes (five studies had sample sizes less than 20) and thus lacked sufficient statistical power to draw definite conclusions. Additionally, follow-up lengths of the studies were either around 3 months or 6 months. Since the volume of uterine leiomyomas decreases overtime and that symptoms can continue to improve until 12 months (34, 35), follow-up periods longer than 6 months may be needed. Confounding is also a major limitation as the majority of included studies did not conduct appropriate covariate adjustments in their analysis.

Lastly, another limitation to note is that no studies directly examined patient-important outcomes such as symptom relief, patient satisfaction, and quality of life (36, 37). As previous studies have shown reduced uterine leiomyoma VR to be associated with increased patient satisfaction, these patient-important outcomes should be considered as additional endpoints in future studies (38, 39). It is recommended in general that prognostic studies include patient-important outcomes, especially since many often fail to do so (40, 41).

There is still a growing interest and need to identify imaging biomarkers for assessing therapeutic responses to UAE and potentially other leiomyoma procedures. In fact, DWI and ADC values have also been examined to determine the treatment response to magnetic resonance imaging-guided high intensity focused ultrasound (32). Other MRI quantitative leiomyoma measurements such as the signal intensities of T2- and T1-weighted sequences and the signal intensity ratio between leiomyoma and myometrium, have also been examined (42, 43).

In conclusion, considering the variability and inconsistency in the current literature, it is currently unclear whether ADC may be useful for predicting treatment response to UAE. A number of limitations associated with using DWI MRIs, such as variability in ADC calculation methods, could explain the heterogeneity among the included studies. Standardization of ADC calculation and interpretation approaches for uterine leiomyomas may therefore be needed.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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Appendix

Supplemental Table. Risk of bias of studies based on the domains of the QUIPs tool (14)

First author, year	Study participation	Study attrition	Prognostic (predictive) factor measurement	Outcome measurement	Study confounding	Statistical analyses & reporting
Ananthakrishnan, 2012 (18)	Moderate	High	Low	High	High	High
Bao, 2017 (28)	Moderate	High	High	High	Moderate	Moderate
Cao, 2014 (19)	Moderate	Low	Moderate	Moderate	High	High
Cao, 2017 (27)	Low	Low	Moderate	Moderate	High	High
Fay, 2013 (20)	High	Low	High	High	High	Moderate
Hecht, 2011 (21)	High	Moderate	High	High	High	Moderate
Kirpalani, 2014 (22)	Low	Low	High	High	High	Moderate
Lee, 2013 (23)	Low	Low	Low	Low	High	Moderate
Liapi, 2005 (24)	High	Low	Moderate	Moderate	High	High
Noda, 2015 (25)	High	Low	Moderate	Moderate	Moderate	Moderate
Sutter, 2016 (26)	Low	Low	Moderate	Moderate	High	Moderate