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REVIEW ARTICLE

Advanced neuroimaging in the clinic: critical appraisal of the evidence base

[1]ADAM Z FINK, [1,2]LISA B MOGIL and [1,3,4,5,6]MICHAEL L LIPTON, MD, PhD

[1]The Gruss Magnetic Resonance Research Center, Albert Einstein College of Medicine, Bronx, NY, USA
[2]SUNY Buffalo School of Medicine and Biomedical Sciences, Buffalo, NY, USA
[3]Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Bronx, NY, USA
[4]The Dominick P Purpura Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY, USA
[5]Department of Radiology, Montefiore Medical Center, Bronx, NY, USA
[6]Departments of Radiology, Albert Einstein College of Medicine, Bronx, NY, USA

Address correspondence to: Dr Michael L Lipton
E-mail: *michael.lipton@einstein.yu.edu*

Fink and Mogil contributed equally to this article and the work it represents.

ABSTRACT

The shortage of high-quality systematic reviews in the field of radiology limits evidence-based integration of imaging methods into clinical practice and may perpetuate misconceptions regarding the efficacy and appropriateness of imaging techniques for specific applications. Diffusion tensor imaging for patients with mild traumatic brain injury (DTI-mTBI) and dynamic susceptibility contrast MRI for patients with glioma (DSC-glioma) are applications of quantitative neuroimaging, which similarly detect manifestations of disease where conventional neuroimaging techniques cannot. We performed a critical appraisal of reviews, based on the current evidence-based medicine methodology, addressing the ability of DTI-mTBI and DSC-glioma to (a) detect brain abnormalities and/or (b) predict clinical outcomes. 23 reviews of DTI-mTBI and 26 reviews of DSC-glioma met criteria for inclusion. All reviews addressed detection of brain abnormalities, whereas 12 DTI-mTBI reviews and 22 DSC-glioma reviews addressed prediction of a clinical outcome. All reviews were assessed using a critical appraisal worksheet consisting of 19 yes/no questions. Reviews were graded according to the total number of positive responses and the 2011 Oxford Centre for evidence-based medicine levels of evidence criteria. Reviews addressing DTI-mTBI detection had moderate quality, while those addressing DSC-glioma were of low quality. Reviews addressing prediction of outcomes for both applications were of low quality. Five DTI-mTBI reviews, but only one review of DSC-glioma met criteria for classification as a meta-analysis/systematic/quantitative review.

INTRODUCTION

Evidence-based medicine (EBM) principles have been widely adopted as the gold standard and even the expected basis for everyday clinical practice. However, adoption of EBM principles in radiology has greatly lagged behind other clinical specialities.[1,2] In fact, the clinical utility of less than one-third of diagnostic imaging procedures is supported by sufficient evidence; as opposed to merely experience and opinion.[2,3] According to EBM standards, systematic reviews constitute the highest level of evidence because they consolidate the evidence of multiple studies rather than relying on the results of one individual study, with its inherent biases, alone.[2,4] Optimal reviews, which adopt EBM practices, provide a comprehensive overview of primary investigations of a specific topic through systematically and comprehensively searching and critically appraising the literature. While many narrative and educational reviews have been published regarding radiological procedures, there is a strong lack of and need for EBM-based systematic reviews in the field of radiology.

Mild traumatic brain injury (mTBI) is a major public health concern, with an annual incidence of more than 1.5 million in the USA.[5,6] Although incidence and prevalence of glioma are much lower than that of mTBI, severe morbidity and mortality are quite high, with 5-year survival rates $<50\%$.[7] In both mTBI and glioma, the most challenging aspect of disease characterization lies at the microscopic level, beyond the reach of conventional CT and MRI. Traumatic axonal injury (TAI) is the primary pathologic feature of mTBI and is not detectable by CT or structural MRI unless, uncommonly, it is associated with haemorrhage.[8] Diffusion tensor imaging (DTI), however, detects TAI as a reduction of the normal directional

coherence of water diffusion in white matter.[8] Glioma infiltrates white matter tracts,[9,10] a phenomenon that conventional contrast-enhanced CT and MRI are unable to fully detect.[9,11] DSC-MRI, however, detects glioma infiltration as elevated CBV due to tumour neoangiogenesis within the normal-appearing white matter of the peritumoral region.[12–14] Both of these techniques may aid in diagnosis, prognosis and treatment.

Currently, the clinical use of DTI and DSC differ greatly. The American College of Radiology appropriateness criteria do not recommend DTI for routine imaging of TBI, although they note that DTI can provide supplemental information about the patterns of injury and prognosis following a head trauma.[15] DSC, however, is recommended for indications including diagnosis and characterization of mass lesions, differential diagnosis, diagnosis of primary neoplasms, surgical planning, therapeutic follow-up, radiation necrosis *vs* recurrent or residual tumour, chemonecrosis *vs* recurrent or residual tumour, pseudoprogression and pseudoresponse.[16] Notably, the ACR appropriateness criteria employ an evidence-rating process different from that proposed by the CEBM and in addition base recommendations on "…clinical judgment and expert consensus as necessary".[17] We therefore applied a standardized EBM approach to specifically assess the actual level of evidence available to support the clinical application of DTI-mTBI and DSC-glioma for both detection of disease pathology and prediction of clinical outcome.

METHODS AND MATERIALS

All methods are based on the most recent (revised 2011) criteria and recommendations of the Oxford Centre for evidence-based medicine (CEBM).[18] Study design, implementation and execution were directly supervised by a board-certified neuroradiologist and in consultation with a senior research librarian. Two graduate medical students appraised the individual reviews after receiving specific training and guidance in the inclusion/exclusion criteria as well as all review and appraisal procedures. Each study was finally reviewed by the entire group to resolve any conflicting assessments.

Delineation of evidence-based medicine questions

We first formulated focused and answerable questions, according to the PICO (Population, Intervention, Control and Outcome) method, in which a list of keywords is developed that describes each category to ensure identification of all evidence addressing the question at hand. These questions were used to guide the search for relevant reviews, which met specific inclusion criteria and were then critically appraised.[19] The following four PICO questions were addressed:

(1) In adults with mTBI, can DTI detect abnormalities in brain tissue?
(2) In adults with glioma, can DSC-MRI detect tumour infiltration into an otherwise normal-appearing brain tissue?
(3) In adults with mTBI, can DTI predict the future clinical outcome?
(4) In adults with glioma, can DSC-MRI predict the future clinical outcome?

Literature search

We conducted systematic searches of the PubMed, Embase and Cochrane databases to identify relevant review articles. A comprehensive list of search terms was created to describe the patient populations and imaging interventions (Table 1) addressed by the PICO questions. Variations of terms were combined to identify all articles that included at least one population and one imaging intervention term. The searches were limited to English language, human species, reviews, meta-analyses or systematic reviews published from 7 January 2009 to 7 January 2014. Search terms for controls and outcomes were not employed in order to prevent excessive limitation of the sample.

After the search was conducted, all listed reviews were analyzed by two raters to confirm relevance and to exclude irrelevant reviews. Irrelevant reviews included paediatric populations, scope outside of this article's focus, publication date beyond the prior 5 years, classification as a non-review article and studies using non-human subjects. Information was extracted from each review, including the following: (1) which PICO question(s) the review addresses, (2) sample size, (3) number of included studies, (4) age and gender of subjects, (5) evidence addressing each PICO question and (6) problems distinguishing evidence for "mild" TBI *vs* "moderate/severe" TBI (for DTI-mTBI reviews only).

Critical appraisal

We developed a critical appraisal worksheet based on the approach of the Oxford CEBM.[18,20] The worksheet (Supplementary Table A) consists of 19 questions that are sorted into the following subgroups: methodological quality ($n = 5$), description of results ($n = 5$), types of included studies ($n = 5$) and the reviews' assessment of included studies ($n = 4$). Each question was answered as yes or no. All questions were framed so that a yes indicated a higher quality of evidence. Where appropriate, specific criteria were formulated to guide responses to the PICO questions. For example, to determine if a review's search strategy was comprehensive, we ascertained: (a) were PubMed, Cochrane and Embase searched? (b) Were MeSH terms and text words included in the search strategy? (c) Was a search of the references from relevant studies performed? (d) Were experts contacted to find unpublished studies?[18,20] (e) To assess a review's inclusion/exclusion criteria, we ascertained: was it clear from the text or citations that the review excluded studies with fewer than four subjects, case reports and non-scientific literature (*e.g.* editorials)?[18,20]

Determining quality of evidence

Each review was appraised separately to determine whether it provided evidence for one or more PICO questions, yielding four separate critical appraisals, addressing (a) DTI-mTBI detection; (b) DTI-mTBI outcome prediction; (c) DSC-glioma detection or (d) DSC-glioma outcome prediction. The quality of evidence presented by each group of literature was assessed using the critical appraisal worksheet. Within each group, the total number of yes responses were summed and converted to percentages (a) for each question, (b) for each of the four subgroups of questions and (c) for the total set of questions. We categorized quality of evidence according to the following scale: high quality (67–100% yes responses), moderate quality (34–66% yes responses) or low quality (0–33% yes responses).

In addition, the quality of evidence presented by each individual review was assessed using three measures: (1) a critical appraisal

Table 1. Search terms

		mTBI-DTI	DSC-glioma
PubMed	Population terms	"mTBI", "tbi", "concussion", "traumatic brain injury"	"brain tumor", "brain tumors", "brain tumour", "brain tumours", "glioma[a]", "glioblastoma[a]"
	Intervention terms	"DTI", "diffusion tensor imaging", "diffusion tensor MRI", "diffusion tensor MRI", "diffusion and MRI"	"Perfusion weighted imaging", "perfusion-weighted imaging", "perfusion weighted MRI", "perfusion-weighted MRI", "perfusion-weighted MRI", "perfusion weighted MRI", "DSC-MRI", "dynamic susceptibility contrast", "DSC", "advanced MRI" "perfusion imaging"
Cochrane	Population terms	"brain injuries," "mTBI," "Brain concussion," "concussion"	"brain tumor," "brain tumors," "brain tumour," "brain tumours," "glioma," "glioblastoma"
	Intervention terms	"diffusion tensor imaging", "diffusion MRI", "DTI"	"perfusion weighted imaging", "perfusion-weighted imaging", "perfusion weighted MRI", "perfusion-weighted MRI", "perfusion weighted MRI", "perfusion-weighted MRI", "perfusion weighted MRI imaging", "perfusion-weighted MRI imaging", "Perfusion Imaging", "dynamic susceptibility contrast," "dynamic-susceptibility contrast", "dynamic susceptibility-contrast", "DSC" "advanced MRI", "dynamic-susceptibility-contrast"
Embase	Population terms	"concussion", "traumatic brain injury", "brain concussion", "tbi," "trauma[a]", "brain injury", "brain injuries"	"brain tumor", brain tumors", "brain tumours", "glioma", glioblasoma", "concussion", "traumatic brain injury", "brain concussion"" "tbi", "trauma[a]", "brain injury", "brain injuries"
	Intervention terms	"diffusion tensor imaging", "dti," "diffusion", "MRI"	"perfusion weighted imaging", "dsc mri", "dynamic susceptibility contrast", "dsc mri," "advanced mr imaging", "perfusion imaging"

DSC-glioma, dynamic susceptibility contrast MRI for patients with glioma; mTBI-DTI, diffusion tensor imaging for patients with mild traumatic brain injury.
Search terms were chosen to describe both the patient population and diagnostic imaging "intervention"; terms varied across databases owing to differences in database scope and vocabularies.

worksheet grade, (2) a quality grade based on the CEBM levels of evidence criteria[21] and (3) classification as a descriptive or systematic/quantitative review. The total number of yes responses for each review was summed and each review was assigned a critical appraisal worksheet grade: A = high quality (67–100% yes responses), B = moderate quality (34–66% yes responses) or C = low quality (0–33% yes responses). In addition, the individual reviews were given a quality grade based on the CEBM levels of evidence criteria[21] and were categorized as descriptive, providing a narrative summary of the primary sources or systematic/quantitative, such as meta-analyses, systematic reviews, Cochrane reviews and quantitative analyses.

The quality of evidence addressing each PICO question was assessed, as well. The number of descriptive and systematic/quantitative reviews that supported, refuted or were inconclusive regarding each PICO question was summed. The number of yes responses achieved by the reviews in each of these groups was averaged. Critical appraisal worksheet grades (A, B and C) were used to describe these averages.

Statistical analysis

To test for differences between summed responses related to DTI-mTBI *vs* DSC-glioma, 2x2 contingency tables were employed. A χ^2 test was used to calculate p-values for contingency tables with expected values ≥ 5.[22,23] Fischer's exact test was used to calculate p-values for contingency tables with expected values <5.[22,23] Significance was set at $\alpha = 0.05$.

Determining strength of evidence

Whereas quality of evidence is based upon responses to the critical appraisal questions, strength of evidence is determined by the total number of studies and subjects supporting a conclusion. The number of studies included in each review, as well as the sample sizes of included studies, were extracted from each article. For reviews that do not explicitly state the number of included studies, we estimated the number of included studies from the text of the review itself (demarcated with an asterisk in Tables 2 and 3). When the subject number could not be determined with reasonable certainty, the term "unclear" is noted in Table 4.

RESULTS

Literature search and inclusion criteria

The search for DTI-mTBI reviews returned 125 review articles (PubMed $n = 36$; Cochrane $n = 7$; Embase $n = 82$) of which 105 unique articles were identified. Excluded articles included: paediatric

Table 2. Sample size and quality of diffusion tensor imaging for patients with mild traumatic brain injury (DTI-mTBI) reviews

mTBI-DTI reviews	Total number of individual studies—detection	Total number of individual studies—prediction of outcome	Total number of subjects—detection	Total number of subjects—prediction	Number of yes responses	Critical appraisal grade	CEBM grade of review quality
Sharp et al (2011)[40]	12[a]	1[a]	Unclear	Unclear	6	C	5
Fitzgerald et al (2011)[27]	15[a]	2[a]	Unclear	Unclear	6	C	5
Aoki et al (2012)[24]	13	0	Unclear	N/A	11	B	1a
Niogi et al (2010)[39]	20	2[a]	438	12	10	B	5
Hulkower et al (2013)[8]	47	0	Unclear	N/A	9	B	2b
Maller et al (2010)[36]	11	0	206	N/A	9	B	1a
Fox et al (2013)[28]	13[a]	1[a]	Unclear	Unclear	6	C	5
Gonzalez et al (2011)[30]	9[a]	3[a]	Unclear	Unclear	2	C	5
Kou et al (2010)[34]	13[a]	0	Unclear	N/A	6	C	5
Gardner et al (2012)[29]	4[a]	0	170	N/A	14	A	1a
Hunter et al (2012)[33]	4[a]	0	Unclear	N/A	5	C	5
Ham et al (2012)[32]	6[a]	2[a]	Unclear	Unclear	3	C	5
Kubal (2012)[35]	3[a]	0	Unclear	N/A	2	C	5
Jeter et al (2013)[6]	4[a]	1[a]	Unclear	Unclear	2	C	5
Grossman et al (2010)[31]	20[a]	2	Unclear	Unclear	6	C	5
Voelbel et al (2012)[43]	18[a]	0	Unclear	N/A	2	C	5
Shenton et al (2012)[41]	32	3[a]	725	45	11	B	5
Bigler (2013)[25]	8[a]	3[a]	Unclear	Unclear	7	B	5
Xiong et al (2014)[44]	5[a]	0	Unclear	N/A	8	B	5
Matis et al (2012)[37]	21[a]	1[a]	Unclear	Unclear	5	C	5
Mechtler et al (2014)[38]	5[a]	0	Unclear	N/A	4	C	5

(Continued)

Table 2. (Continued)

mTBI-DTI reviews	Total number of individual studies—detection	Total number of individual studies—prediction of outcome	Total number of subjects—detection	Total number of subjects—prediction	Number of yes responses	Critical appraisal grade	CEBM grade of review quality
Dimou et al (2014)[26]	2[a]	1[a]	Unclear	Unclear	4	C	5
Van Boven et al (2009)[42]	7[a]	0	Unclear	N/A	7	B	5

CEBM, Centre for evidence-based medicine; DTI, diffusion tensor imaging; mTBI, mild traumatic brain injury; N/A, not applicable.
"Unclear" denotes total number could not be calculated because not all subjects were enumerated in the text.
Review quality was graded using the CEBM levels of evidence and by calculating the number of the yes responses on the critical appraisal worksheet (Supplementary Table A) for each review.
[a]The number of primary studies included in each review and the sample size of each primary study, as reported in the review or estimated from its text.

($n = 13$); beyond the scope (e.g. populations other than those with mTBI, imaging techniques other than DTI; n = 68); >5 years since publication ($n = 2$); or not a review ($n = 2$). 20 review articles remained (PubMed and Embase overlap n=11; PubMed alone n = 6; Embase alone $n = 3$; Cochrane $n = 0$).

The search for DSC-glioma reviews returned 148 articles (PubMed $n = 37$; Cochrane $n = 16$; Embase $n = 95$) of which 121 unique articles were identified. Excluded articles included: paediatric ($n = 5$); beyond the scope (*e.g.* populations other than glioma, imaging techniques other than DSC; $n = 75$); >5 years since publication ($n = 6$); not a review ($n = 10$); or non-human species ($n = 1$). 24 review articles remained (PubMed and Embase overlap $n = 17$; PubMed alone $n = 20$; Embase alone $n = 6$; Cochrane $n = 0$).

Cross-checking the reference lists of these articles, we identified three additional DTI-mTBI and two additional DSC-glioma reviews. Thus, 23 DTI-mTBI[6,8,24–44] and 26 DSC-glioma[7,9,12,45–67] review articles were included in the analysis.

Critical appraisal worksheet

The total percentages of yes responses for each subgroup and the total set of critical appraisal questions are shown in Figure 1. Percentages of yes responses for each individual critical appraisal question are shown in Supplementary Figures A–D.

According to the total percentage of yes responses to the critical appraisal questions, reviews addressing DTI-mTBI detection are of moderate quality, while those addressing DSC-glioma detection are of low quality. Reviews addressing outcome prediction for both DTI-mTBI and DSC-glioma achieved overall low quality. There was a significant difference between the total number of yes responses to the critical appraisal worksheet questions for detection reviews addressing DTI-mTBI *vs* DSC-glioma, in favour of DTI-mTBI (Table 5). Each DTI-mTBI ($n = 12$) and DSC-glioma ($n = 22$) review that addressed outcome prediction also addressed detection of brain abnormality. Therefore, these studies are included in the critical appraisal. Consideration of these reviews as a separate group confirmed a significant difference between the sums of responses to the critical appraisal questions, in favour of DTI-mTBI (Table 5).

The critical appraisal subgroups and questions for which the greater number of yes responses achieved by DTI-mTBI reviews were statistically significant are delineated in Table 5. A detailed comparison of the critical appraisal results reveals the following: DTI-mTBI and DSC-glioma reviews each demonstrated low quality in the subgroup, "Methodological Quality", with the exception of achieving high quality for the percentage of reviews that addressed a specific question (Supplementary Figure A).

In the subgroup "Description of Results", DTI-mTBI reviews were of moderate quality and DSC-glioma reviews were of low quality regarding the percentage of reviews that clearly depicted the results of each included study. DTI-mTBI and DSC-glioma reviews were both of high quality for percentage of reviews that considered reasons for variation among results and provided a clear bottom line. DTI-mTBI reviews demonstrated high quality and DSC-glioma reviews demonstrated moderate quality for noting heterogeneity or homogeneity among results. Both DTI-mTBI and DSC-glioma reviews were of low quality regarding the percentage of reviews that presented confidence intervals with all results (Supplementary Figure B).

DTI-mTBI and DSC-glioma demonstrated low quality for each question in the subgroup "Types of Included Studies". Notably, <5% of DSC-glioma detection reviews and no DSC-glioma outcome prediction review garnered yes responses for any of the questions in this subgroup. <25% of reviews addressing each imaging modality noted the study design of all included studies or the exclusion of low-quality study designs and non-scientific literature (Supplementary Figure C). However, three DTI-mTBI reviews[25,39,44] and two DSC-glioma reviews[62,64] describe the design of some but not all included studies.

Table 3. Assessment of number of primary studies, number of subjects and quality of dynamic susceptibility contrast MRI for patients with glioma (DSC-glioma) reviews

Sample size and quality for DSC-glioma reviews							
DSC-glioma reviews	**Total number of individual studies—detection**	**Total number of individual studies—prediction of outcome**	**Total number of subjects—detection**	**Total number of subjects—prediction of outcome**	**Number of yes reponses**	**Critical appraisal grade**	**CEBM grade of review quality**
Nelson (2011)[59]	9[a]	3[a]	unclear	Unclear	3	C	5
Kao et al (2013)[56]	3[a]	0	Unclear	0	3	C	5
Lee et al (2013)[58]	9[a]	0	Unclear	0	3	C	5
Gao et al (2011)[52]	5[a]	0	Unclear	0	3	C	5
Deng et al (2013)[7]	7	0	174	0	15	A	1b
Law (2009)[57]	3[a]	3[a]	Unclear	Unclear	1	C	5
Romano et al (2012)[64]	13[a]	12[a]	Unclear	Unclear	4	C	5
Faehndrich et al (2011)[12]	9[a]	2[a]	Unclear	Unclear	6	C	5
Dhermain et al (2010)[47]	16[a]	4[a]	Unclear	Unclear	6	C	5
Hochberg et al (2012)[54]	5[a], 5[a] (Unclear)	2[a]	Unclear	Unclear	2	C	5
Fatterpekar et al (2012)[50]	7[a]	5[a]	171	Unclear	4	C	5
Ahmed et al (2014)[9]	3[a] (Unclear)	1[a]	Unclear	Unclear	3	C	5
Vincentelli et al (2012)[67]	3[a]	1[a] (Unclear)	Unclear	Unclear	3	C	5
Bruzzone et al (2012)[45]	12[a], 4[a] (Unclear)	1[a]	Unclear	Unclear	3	C	5
Pillai et al (2010)[61]	9[a]	8[a]	Unclear	Unclear	3	C	5
Cha (2009)[46]	5[a]	2[a]	Unclear	Unclear	3	C	5
Price (2010)[63]	20[a]	6[a]	Unclear	Unclear	5	C	5
Peet et al (2012)[60]	6[a]	3[a]	Unclear	Unclear	4	C	5
Gerstner et al (2010)[53]	3[a]	1[a]	Unclear	Unclear	3	C	5
Shiroishi et al (2011)[66]	18[a]	5[a]	Unclear	Unclear	5	C	5
Fussell et al (2013)[51]	23[a], 3[a] (Unclear)	8[a]	Unclear	Unclear	5	C	5
Essig et al (2013)[49]	2[a], 18[a] (Unclear)	5[a] (Unclear)	Unclear	Unclear	5	C	5
Schuknecht et al (2012)[65]	3[a]	6[a]	Unclear	Unclear	3	C	5
Pope et al (2011)[62]	4	5	204	236	7	B	5
Essig et al (2012)[48]	2[a]	3[a]	Unclear	Unclear	3	C	5
Hygino da Cruz et al (2011)[55]	1[a]	2[a]	Unclear	Unclear	3	C	5

CEBM, centre for evidence-based medicine.
"Unclear" denotes total number could not be calculated because not all subjects were enumerated in the text.
Review quality was graded using the CEBM levels of evidence and by calculating the number of the yes responses on the critical appraisal worksheet (Supplementary Table A) for each review.
[a]The number of primary studies included in each review and sample size of each primary study, as reported in the review or estimated from its text.

For the subgroup, "Reviews' Quality Assessment of Included Studies", both DTI-mTBI and DSC-glioma reviews were of moderate quality with respect to the percentage of reviews that discussed limitations of their articles or of the MRI technique on which they reported. DTI-mTBI reviews showed moderate quality for noting limitations of included studies, while DSC-MRI reviews showed low quality. All reviews demonstrated low quality with respect to discussion of quality assessment and in specification of the number of subjects in each included study (Supplementary Figure D).

Classification and grading of individual review's overall quality

We classified 5/23 DTI-mTBI detection reviews[8,24,29,34,36] and 1/26 DSC-glioma detection reviews[7] as systematic/quantitative reviews (Figure 2). We classified all reviews addressing outcome prediction, whether DTI-mTBI or DSC-glioma, as descriptive (Figure 2), although some quantitative reviews did incorporate longitudinal studies.[8]

Regarding CEBM review quality grades for detection reviews, three DTI-mTBI reviews were given a grade of 1a and one review was given a grade of 2b (Table 4). One DSC-glioma review was assigned a grade of 1b (Table 2). The remaining detection reviews and all reviews addressing prediction of outcome were assigned a grade of 5 (Table 4, Table 2).

Regarding critical appraisal worksheet grades for DTI-mTBI detection reviews, 1 review achieved Grade A,[29] 8 reviews achieved Grade B[8,24,25,36,39,41,42,44] and 14 reviews achieved Grade C.[6,26–28,30–35,37,38,40,43] Of the reviews of DTI-mTBI outcome prediction, three reviews achieved Grade B[25,39,41] and the remaining reviews were Grade C.[6,26–28,30–32,37,40] Of the reviews of DSC-glioma detection, 1 review achieved Grade A,[7] 1 review achieved Grade B[62] and 24 reviews achieved Grade C.[9,12,45–61,63–67] Of the reviews of DSC-glioma prediction of outcome, 1 review achieved Grade B[62] and the remaining reviews were Grade C.[9,12,45–51,53–55,57,59–61,63–67]

Strength of evidence presented by individual reviews

Our ability to assess the strength of evidence was impeded by the dearth of reviews that explicitly stated the number of studies included or the number of subjects reported by each included study. Reviews that explicitly state the number of studies included are as follows: 5 of 23 DTI-mTBI detection reviews,[8,24,36,39,41] 1 of 12 DTI-mTBI outcome prediction reviews,[31] 2 of 26 DSC-glioma detection reviews[7,62] and 1 of 22 DSC-glioma outcome prediction reviews[62] (Tables 2 and 3).

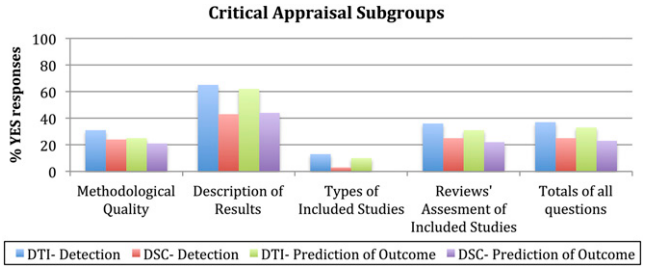
Generally, fewer reviews explicitly stated the number of subjects reported by included studies, as follows: 4 of 23 DTI-mTBI

Table 4. Study conclusions and strength of evidence

Review category	Systematic/quantitative/meta-analyses			Descriptive reviews		
Response	Y	N	U	Y	N	U
In adults with mTBI, can DTI detect abnormalities in the brain tissue?						
	5 (B)	0	0	12 (B)	0	6 (C)
In adults with mTBI, can DTI predict the future clinical outcome?						
	0	0	0	0	0	12
In adults with glioma, can DSC-MRI detect tumour infiltration into an otherwise normal-appearing brain tissue?						
Tumour grade	0	0	0	15 (C)	0	5 (C)
Differential diagnosis	0	0	0	8 (C)	0	2 (C)
Monitoring response to therapy	0	0	0	0	2 (C)	4 (C)
Biopsy guidance	0	0	0	5 (C)	0	1 (C)
Pseudoprogression	0	0	0	5 (C)	1	5 (C)
Detecting tumour recurrence from radiation necrosis	1 (A)	0	0	9 (C)	1	3 (C)
In adults with glioma, can DSC-MRI predict future clinical outcome?						
Tumour progression	0	0	0	9 (C)	0	5 (C)
Survival	0	0	0	4 (C)	0	2 (C)

DSC-MRI, dynamic susceptibility contrast MRI; DTI, diffusion tensor imaging; mTBI, mild traumatic brain injury; N, not supporting; U, unclear; Y, supporting.
Reviews were categorized into one of two groups: systematic/meta-analysis/quantitative or descriptive. Conclusions of the diffusion tensor imaging for patients with mild traumatic brain injury and dynamic susceptibility contrast MRI for patients with glioma (DSC-glioma) are shown, specifying the number of reviews supporting (Y), not supporting (N) or unclear (U) for each question, with the quality of the evidence shown in parentheses. To grade quality, the number of yes responses to critical appraisal questions was averaged for each group of reviews with the same conclusion. The average of yes responses was scaled with the quality of evidence scale and assigned a letter value of A (67–100% yes responses), B (34–66% yes responses) or C (0–33% yes responses). Reviews of DSC-glioma assessed effectiveness for multiple specific clinical outcomes and are therefore further subdivided. A fully referenced version of this table is available as Supplementary Table B.

Figure 1. Critical appraisal subgroups: percentages of "yes" and "no" responses were calculated for each subgroup and for the total set of critical appraisal questions. DSC, dynamic susceptibility contrast MRI; DTI, diffusion tensor imaging. For colour image see online.



detection reviews,[29,36,39,41] 2 of 12 DTI-mTBI prediction of outcome reviews,[39,41] 3 of 26 DSC-glioma detection reviews[7,50,62] and 1 of 22 DSC-glioma prediction of outcome reviews.[62] In addition, where reviews included both our target population and other populations (*e.g.* paediatrics, moderate or severe TBI, tumours other than glioma), determining the relevant component of a review may have further limited this assessment.

How well does the evidence address the Population, Intervention, Control and Outcome questions?

All 5 systematic/quantitative/meta-analysis reviews and 66.7% (12/18) of the descriptive reviews on DTI-mTBI detection supported the use of DTI in the detection of abnormality in the brain tissue. While an average critical appraisal worksheet grade of B was assigned to the systematic/quantitative/meta-analysis reviews in support, it is important to note that it includes one Grade A article.[29] All 12 descriptive reviews addressing prediction of future clinical outcomes were inconclusive with an average critical appraisal worksheet grade of C (Table 3).

DSC-glioma detection reviews addressed the ability of DSC to distinguish tumour infiltration from an otherwise normal-appearing brain tissue in distinct settings. The single systematic/quantitative review addressing DSC-glioma detection, which achieved Grade A, supported the ability of DSC to detect tumour recurrence from radiation necrosis.[7] Nine descriptive reviews also supported DSC for the differentiation of tumour recurrence and radiation necrosis, including one Grade B review;[62] one descriptive review was inconclusive and three descriptive reviews refuted the efficacy of DSC for this purpose. DSC-glioma detection reviews also addressed DSC for multiple purposes, including detection of tumour infiltration into a "normal-appearing" brain tissue, for determining tumour grade, monitoring tumour response to therapy and guiding biopsy. The conclusions of these studies are presented in Table 3.

DSC-glioma reviews addressing outcome prediction which are descriptive in nature and achieved an average grade of C addressed DSC's ability to predict tumour progression and survival in patients with glioma. Of the descriptive reviews that addressed DSC for prediction of tumour progression, 64.3% (9/14) reviews were supportive and 35.7% (5/14) reviews were inconclusive. 66.7% (4/6) of descriptive reviews supported the use of DSC to predict survival, and the remaining reviews were inconclusive (Table 3, Supplementary Table B).

DISCUSSION

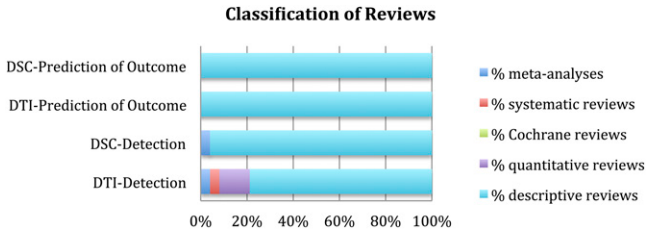
In this article, we conducted an EBM systematic review to assess two areas where advanced quantitative MRI methods are of great interest for the detection of pathology in an otherwise normal-appearing brain tissue and for the prediction of outcome. We identified multiple reviews incorporating a large number of primary research studies addressing DTI-mTBI and DSC-glioma. The quality of the evidence presented by the included reviews in support of each application vary significantly; DTI-mTBI reviews and the evidence they present are, overall, of higher quality than DSC-glioma reviews. While DSC-glioma detection reviews are similar in quality and strength to DTI-mTBI detection reviews in some areas, they do not present stronger evidence than DTI-mTBI reviews in any topic area on

Table 5. In all cases, the number of yes responses was greater for diffusion tensor imaging for patients with mild traumatic brain injury (DTI-mTBI) than for dynamic susceptibility contrast MRI for patients with glioma (DSC-glioma)

Critical appraisal worksheet "yes" responses for DTI-mTBI *vs* DSC-glioma reviews		
Question	Detection	Prediction of outcome
Overall outcome of critical appraisal questions		
Total responses to all questions	0.0002[a]	0.0114[a]
Critical appraisal subgroups		
Description of results	0.0010[a]	0.0325[a]
Types of studies included	0.0076[a]	0.0020[a]
Individual questions		
Did the author note any homogeneity or heterogeneity among the results?	0.0032[a]	0.0297[a]
Does the review mention any limitations on individual studies?	0.0002[a]	0.0007[a]

[a] $p < 0.05$.

Figure 2. Classification of reviews: classification of diffusion tensor imaging for patients with mild traumatic brain injury and dynamic susceptibility contrast MRI for patients with glioma articles into types of reviews. DSC, dynamic susceptibility contrast MRI; DTI, diffusion tensor imaging. For colour image see online.



the critical appraisal worksheet. Although the greater number of total yes responses achieved by DTI-mTBI outcome prediction compared with DSC-glioma is statistically significant, reviews addressing outcome prediction for both imaging techniques demonstrated low quality of evidence overall.

A greater number of DTI-mTBI detection reviews were classified as systematic/quantitative (5/23 reviews) than DSC-glioma detection reviews (1/26 reviews). The remaining reviews were descriptive in nature, providing a narrative of several primary research studies without application of EBM methods or criteria to substantiate their conclusions (Table 3, Supplementary Table B). Although a small number of these reviews incorporate elements of a systematic review, their overall structure corresponds best to Level 5 on the CEBM levels of evidence, defined as an "expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles".[21]

The efficacy of DTI in detecting mTBI is supported by a number of reviews, including one Grade A article[29] and four Grade B articles.[8,24,34,36] A single Grade A review supports DSC, but only for the very specific application of differentiating tumour recurrence from radiation necrosis.[7] In addition, a greater number of Grade B reviews support DTI for detecting brain abnormality in patients with mTBI compared with only one Grade B review in support of DSC for detecting glioma. Although only descriptive articles with an average Grade C (including three Grade B DTI-mTBI articles and one Grade B DSC-glioma article) discussed outcome prediction, it is important to note that no reviews supported the use of DTI in predicting clinical outcomes, while nine articles support the use of DSC in predicting tumour progression and four reviews support the use of DSC in predicting survival time.

Our assessments are most complete regarding quality of evidence measured by our critical appraisal worksheet results. We also assessed, but could not fully characterize, differences in the strength of the evidence presented by mTBI-DTI *vs* DSC-glioma reviews because many of the reviews did not explicitly state the number of primary studies and/or subjects encompassed by each review. This deficiency is more severe for DSC-glioma reviews. Thus, while we characterize the strength of evidence as more robust for DTI-mTBI, this conclusion is limited by the greater absence of detail included in DSC-glioma reviews.

The assessments we report address the body of literature as a whole. The differences are thus not a specific critique of any individual review and certainly not a specific critique of any individual research study included in the reviews we analyzed.

Several limitations to our study must be considered. First, although our methods for review of the articles were highly standardized and we relied on the consensus of two reviewers, with a third arbiter for ambiguous cases, the possibility of reviewer bias cannot be absolutely excluded. Second, our findings are, of course, limited to the scope of the reviews we included. We cannot, for example, generalize our findings to the assessment of children, nor can we provide an assessment of DTI for non-traumatic injury or DSC efficacy for the assessment of tumours other than glioma. Importantly, however, the very heterogeneity of these review articles, which reflects heterogeneity across the primary research studies they assess, underscores the robustness of the evidence base from which salient conclusions can be supported despite variability across studies. Third, owing to the all-or-nothing (only "yes" and "no" were accepted as responses) fashion in which five of the critical appraisal questions were asked, reviews that partially addressed these questions were grouped with "no" responses. We thus may underestimate the strength of the evidence. Reviews with such partial responses included: "was the search strategy comprehensive", (DTI-mTBI, $n = 16$;[6,25–28,30–35,37,38,40,42,43] DSC-glioma, $n = = 23$[7,9,12,45,46,48–51,53–59,61–67]), "were the results of all individual studies clearly described", (DTI-mTBI, $n = 5$;[26,31,38,40,43] DSC-glioma, $n = 11$[45–48,52,53,55,57,63,64,66]), "are all of the results presented with confidence intervals", (DTI-mTBI $n = 1$;[34] DSC-glioma $n = 4$[50–52,65]), "does it state the study design of all included articles" (DTI-mTBI, $n = 3$;[25,39,44] DSC-glioma, $n = 3$[62,64]) and "does it specify the number of subjects for all included studies" (DTI-mTBI, $n = 11$;[8,25,27,28,31,34,37,38,40,42,44] DSC-glioma, $n = 8$[47,50,51,57,60,61,63,64]).

CONCLUSION

The evidence supporting DTI-mTBI for the detection of brain abnormalities is substantially more robust than that supporting DSC-glioma, although evidence supporting the prediction of outcome for either application is similarly quite limited. This disparity in the abundance, quality and strength of evidence is particularly notable in light of its contrast with the recommendations of consensus statements, such as the ACR appropriateness criteria. Developing future clinical recommendations and guidelines on a solid and rigorous EBM foundation can serve to move the practice of radiology towards the mainstream of evidence-based medicine.

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