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FULL PAPER

Standard-*b*-value vs low-*b*-value DWI for differentiation of benign and malignant vertebral fractures: a meta-analysis

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Objective: To determine the comparative diagnostic performance of standard-*b*-value ($\geq 500 \text{ mm}^2$) vs low-*b*-value ($< 500 \text{ mm}^2$) diffusion-weighted imaging (DWI) for discriminating malignant from benign vertebral compression fractures.

Methods: 12 studies with a total of 350 malignant and 312 benign vertebral fractures were included.

Results: The apparent diffusion coefficient (ADC) value of benign vertebral compression fractures was lower than that of malignant vertebral compression fractures ($SMD = 1.81$, 95% CI 0.98 to 2.64 $Z = 4.27$, $p < 0.05$). ADC value difference was more pronounced in the group of low-*b*-value DWI ($SMD = 2.31$, 95% CI 1.02 to 3.60 $Z = 3.51$, $p < 0.05$) than in the group of standard-*b*-value DWI ($SMD = 1.38$, 95% CI 0.18 to 2.59 $Z = 2.25$, $p < 0.05$). Ethnicity stratified analysis demonstrated higher ADC values in benign vertebral compression fractures in comparison to malignant tissues

in both the Asian and Caucasian subgroups (Asians: $SMD = 2.400$, 95%CI 1.45 to approximately 3.35, $p < 0.05$; Caucasians: $SMD = 0.592$, 95 % CI -0.848 to approximately 2.032, $p < 0.05$). And the ADC value difference was more pronounced in the Asian subgroup.

Conclusion: ADC value appears to be a reliable method to differentiate benign from malignant fractures. Low-*b*-value DWI was more a valuable parameter than standard-*b*-value DWI for discriminating malignant from benign vertebral compression fractures. And the diffusion characteristics of the benign vertebral fractures such as osteoporosis, trauma and infection have rarely been investigated separately.

Advances in knowledge: The use of low-*b*-value DWI for differentiation of benign and malignant vertebral fractures is recommended.

Metastases to the spine occur in up to 10% of patients with primary neoplasms. However, it has been estimated that up to one-third of vertebral compression fractures in patients with known malignancies are benign.^{1–5} Although diagnostic imaging has made remarkable progress in recent years, it remains difficult to differentiate benign and malignant vertebral fractures. Appropriate treatment of vertebral fractures requires knowledge of the cause of the fracture.^{6,7}

Diffusion-weighted imaging is a sensitive technique that allows for noninvasive characterization of biological tissues on the basis of the diffusion of water molecules.⁸ Diffusion-weighted imaging (DWI) and apparent diffusion coefficients (ADCs) have been studied in variable clinical situations, including grading of tumours and assessment of tumour response.⁹ Theoretically, DW imaging with a higher *b*-value yields better contrast with its reflection of more tissue diffusivity and less T2 shine-through effect.⁹ Perfusion effects which occur at low *b* values, so a technique which focuses

more on low *b* value information will have correspondingly more perfusion information.¹⁰

DWI has proven to be a useful method in the differential diagnosis of benign and malignant vertebral compression fractures.^{11–15} However, the results varies across studies. The present systematic review and meta-analysis aim to summarise and combine the published data on diffusion-weighted imaging for discriminating malignant from benign vertebral compression fractures. We conducted a subgroup meta-analysis of *b*-value ≥ 500 and *b*-value < 500 used for ADC calculation. Ethnicity stratified analysis was also performed.

METHODS AND MATERIALS

Search strategy

The initial database (the Chinese Biological Medicine, Pubmed, MEDLINE and EMBASE databases) search identified 1518 relevant articles that were published including till

Table 1. Main characteristics of the studies evaluating the performance of diffusion-weighted imaging for the differentiation of vertebral compression fractures

Number	Study name	Patient population	Published year	MRI unit	Field (T)	Pulse	TR	TE	<i>b</i> factors, No	<i>b</i> factor (Max)	<i>b</i> factor (Min)	FS	<i>b</i> factor (Max)	<i>b</i> value used for ADC calculation
1	Chan et al ¹⁴	Asians	2002	GE	1.5	SS-SE-EPI	8000	92	4	1000	200	yes	1000	1000
2	Zhou et al ¹¹	Caucasians	2002	Philips	1.5	SS-SE-EPI	1648	63	3	250	150	NA	250	<250
3	Maeda et al ¹³	Asians	2003	GE	1.5	LS-EPI	2093–3498	70.5	2	1000	5	NA	1000	1000
4	Tang et al ¹²	Asians	2007	Philips	1.5	SS-SE-EPI	1400	100	8	800	100	yes	800	300
5	Balliu et al ¹⁵	Caucasians	2009	Philips	1.5	multishot SE-EPI	1600	95	2	500	0	yes	500	500
6	Lu lu and Song-bai ¹⁶	Asians	2013	GE	3.0	SS-SE-EPI	2800	57	6	800	300	NA	800	300
7	Zengxu and Zhou ¹⁷	Asians	2012	GE	1.5	SS-EPI	3000–4000	53–80	1	300	300	yes	300	300
8	Chunlong ¹⁸	Asians	2013	GE	1.5	SE-EPI	11500	88.8	5	1000	200	NA	1000	400
9	Jiu-ming ¹⁹	Asians	2013	GE	1.5	SE-EPI	1500	30	1	1000	1000	NA	1000	1000
10	Yan ²⁰	Asians	2008	Philips	1.5	SE-EPI	2000	65	1	500	500	NA	500	500
11	Pozzi ²¹	Caucasians	2012	Siemens	1.5	SS-SE-EPI	NA	NA	1	800	800	NA	800	800
12	Geith et al ²²	Caucasians	2014	Siemens	1.5	SS-SE-EPI	3000	72	4	600	100	yes	600	100/400

ADC, apparent diffusion coefficient; EPI, echo planar imaging; FS, fat suppression; NA, not available; SE, single echo; SS, single shot; TE, echo time; TR, repetition time.

Jan 2015. The literature search was performed with the following terms: vertebral compression fractures and diffusion-weighted imaging, vertebral compression fractures and DWI, fractures and diffusion-weighted imaging, fracture and diffusion-weighted imaging, fractures and DWI, fracture and DWI. The research was limited to articles concerning humans with an abstract in English and Chinese.

Study inclusion criteria

Two independent reviewers reviewed the abstracts from all the citations. Inclusion criteria were applied to the retrieved articles independently by the reviews. Studies were included in this analysis (1) if the diagnostic criteria of the malignant or benign vertebral compression fractures were clearly reported; (2) if DWI imaging was obtained to evaluate malignant or benign vertebral compression fractures; (3) if DWI acquisition procedures were clearly stated; (4) by the presence of ADC value [mean $\pm$ standard deviation (SD)], which could be extracted from the original study.

Data collection

The following data were extracted from all the studies that met the inclusion criteria: the study name, published year, MR modalities used (GE, Siemens and Philips), pulse, repetition time (TR, ms), echo time (TE, ms), the number of *b* factors, *b*-value (min) and *b*-value (max) (s mm^{-2}), number of malignant and benign vertebral compression fractures, ADC value of malignant and benign vertebral compression fractures, ADC SD of malignant and benign vertebral compression fractures (Tables 1 and 2).

Statistical analysis

All meta-analyses were performed using Stata® (v. 12.0; Stata-Corp, College station, TX). We pooled and statistically compared ADC data from malignant or benign vertebral compression fractures. Meta-analysis of continuous outcomes uses weighted mean difference (SMD). This heterogeneity was assessed by using Cochran Q test and the I-square test. When the Cochran Q test was significant or I-square value was $>50\%$, the heterogeneity exists and random effect model (DerSimonian-Laird method) should be selected instead of fixed effect model (Mantel-Haenszel method) for calculation of pooled data. Forest plots were drawn to show a visual representation of the amount of variation between different groups. Publication bias was assessed. For all tests, *p*-values <0.05 were regarded as significant.

RESULTS

Study selection and data extraction

The literature search and study selection flow chart is displayed in Figure 1. The initial database search identified relevant articles that were published including till Jan 2015. The literature search from our previous study yielded 1518 articles, of which 112 were reviewed in abstract, and from them 29 were further reviewed in full text. Of these, 12 studies were eligible for inclusion.^{11–22}

Description of studies

12 studies with a total of 350 malignant vertebral compression fractures and 312 benign vertebral compression fractures were included in this meta-analysis (# 1–12) Figures 2 and 3.

Table 2. Main characteristics of the studies evaluating the performance of diffusion-weighted imaging for the differentiation of vertebral compression fractures

Number	N (benign)	Osteoporosis	Trauma	Infection	ADC mean (benign)	ADC SD (benign)	N (malignant)	Metastases	Multiple myeloma	ADC mean (malignant)	ADC SD (malignant)
Chan et al ¹⁴ 2002	31	25	0	6	1.94	0.35	18	18	0	0.82	0.2
Zhou et al ¹¹ 2002	12	NA	NA	NA	0.32	0.05	15	15	0	0.19	0.03
Maeda et al ¹³ 2003	20	NA	NA	0	1.21	0.17	16	16	0	0.92	0.2
Tang et al ¹² 2007	18	4	14	0	2.23	0.21	27	27	0	1.04	0.03
Balliu et al ¹⁵ 2009	30	0	16	14	1.46	0.64	15	15	0	0.92	1.3
Lu lu and Song-bai ¹⁶ 2013	23	NA	NA	0	1.75	0.41	22	18	4	1.11	0.33
Zengxu and Zhou ¹⁷ 2012	47	NA	NA	NA	0.7	0.2	100	NA	NA	0.45	0.11
Chunlong ¹⁸ 2013	21	0	0	21	1.42	0.58	43	43	0	1.46	0.5
Jiu-ming ¹⁹ 2013	30	NA	NA	0	1.8	0.312	20	20	0	1.3	0.241
Yan et al ²⁰ 2008	44	NA	NA	0	1.42	0.26	31	31	0	0.91	0.17
Pozzi ²¹ 2012	10	10	0	0	0.646	0.368	23	23	0	1.241	0.4
Geith et al ²² 2014	26	26	0	0	1.76	1.84	20	20	0	1.31	1.42

ADC, apparent diffusion coefficient; SD, standard deviation.

Figure 1. Selection process of the articles. Pooled analysis. ADC, apparent diffusion coefficient; SD, standard deviation.

Eleven studies used 1.5-T field strength (# 1–5, 7–12) while one study used 3.0 T (# 6). The TE of the DWI varied considerably in the studies ranging from 30 (# 9) to 100 (# 4). One study did not provide information on TE (# 11). The TR of the DWI varied considerably in the studies ranging from 1500 (# 9) to 11,500 (# 6). One study did not provide information on TR (# 11). Six studies used SSEPI sequence studies (# 1–2, 4, 6–7, 11–12). Six studies (# 1, 3–6) used a sequence with maximum of b factor in the range of 500–1000 ms. Ten studies (# 1, 3, 4–6, 8–12) used a sequence with maximum of b factor in the range of 500–1000 ms. Nine studies (# 1–8, 12) used a sequence with minimum of b factor in the range of 0–500 ms. Six studies (# 2, 4, 6–8, 12) used a sequence with b factor in the range of 0–500 ms for ADC calculation while six studies (# 2, 4, 6–8, 12) used a sequence with b factor in the range of ≥ 500 for ADC calculation (# 1, 3, 5, 9–11). Seven studies did not provide information on fat-suppressed technique (# 2–3, 5 and 7–10). The results of all analyses are reported in [Tables 1](#) and [2](#).

Synthesis of general diagnostic parameters

The ADC value of benign vertebral compression fractures was lower than that of malignant vertebral compression fractures ($SMD = 1.81$, 95% CI 0.98 to 2.64 $Z = 4.27$, $p < 0.05$). Significant heterogeneity between studies was noted (all $p < 0.05$). Publication bias was not present ($t = 1.51$, $p = 0.162$).

Subgroup meta-analysis of standard-b-value DWI (b value ≥ 500) and low-b-value DWI (b value < 500) used for ADC calculation

We conducted a subgroup meta-analysis of b factor ≥ 500 used for ADC calculation based on 6 studies, including 123 malignant vertebral compression fractures and 165 benign vertebral compression fractures. The ADC value of benign vertebral compression fractures was lower than that of malignant vertebral compression fractures ($SMD = 1.38$, 95% CI 0.18 to 2.59 $Z = 2.25$, $p < 0.05$).

We conducted a subgroup meta-analysis of b factor < 500 used for ADC calculation based on 6 studies, including 227 malignant vertebral compression fractures and 147 benign vertebral compression fractures. The ADC value of benign vertebral compression fractures was lower than that of malignant vertebral

compression fractures ($SMD = 2.31$, 95% CI 1.02 to 3.60 $Z = 3.51$, $p < 0.05$).

ADC value difference was more pronounced in the group of low-b-value DWI ($SMD = 2.31$, 95% CI 1.02 to 3.60 $Z = 3.51$, $p < 0.05$) than in the group of standard-b-value DWI ($SMD = 1.38$, 95% CI 0.18 to 2.59 $Z = 2.25$, $p < 0.05$).

Subgroup meta-analysis of patient population (Asians and Caucasians)

Patient population (ethnicity) stratified analysis demonstrated higher ADC values in benign vertebral compression fractures in comparison to malignant tissues in both the Asian and Caucasian subgroups (Asians: $SMD = 2.400$, 95% CI 1.447–3.354, $p < 0.05$; Caucasians: $SMD = 0.592$, 95% CI -0.848 –2.032, $p < 0.05$). ADC value difference was more pronounced in the Asian subgroup.

DISCUSSION

Vertebral compression fractures are common, and it is sometimes difficult to determine whether the cause is benign or malignant.^{23,24} Accurate diagnosis linked to appropriate treatment is important. Preliminary data using diffusion-weighted imaging of vertebral compression fractures showed a reduced water mobility in pathological fractures. Based on calculations of the relevant data available in the currently published articles, our systematic review and meta-analyses showed that the ADC value of benign vertebral compression fractures was lower than that of malignant vertebral compression fractures. ADC value difference was more pronounced in the group of b-value < 500 than in the group of b-value ≥ 500 . All these demonstrated that DWI and ADC value was useful for differentiation between malignant and benign vertebral compression fractures.

We need to admit that if a meta-analysis can give a best cut-off level, the results might be more informative. The reported mean ADC values of malignant and benign vertebral fractures in our meta-analysis ranged from 0.19 to 1.46 and 0.32 to $2.23 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, respectively. Unfortunately, a threshold level was not proposed by any study using DW imaging in our meta-analysis. Under such circumstance, a best cut-off level could not be identified by meta-analysis. This is an intrinsic deficiency of meta-analysis for diagnostic accuracy test.²⁵ Based on individual raw data in our meta-analysis, a reasonable threshold for malignancy seems to be an ADC value of $1.4 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ or less (OR = 7.13). Further prospective studies need to be completed in larger scales to validate our results.

The high cellularity of malignant vertebral compression fractures increases intracellular volume fraction relative to the interstitial space. Because the water diffusion coefficient is approximately 10 times lower in the intracellular than in the extracellular space, this should lower ADC values of malignant vertebral compression fractures. However, the cellularity of benign fractures can be lower than that of malignant vertebral compression fractures, because of the increased interstitial space associated with oedema in the acute phase. Correspondingly, we found that the ADC value of benign vertebral compression fractures was lower than that of malignant vertebral compression fractures.

Figure 2. The apparent diffusion coefficient (ADC) value of benign vertebral compression fractures (a) was lower than that of malignant vertebral compression fractures ($SMD = 1.81$, 95% CI 0.98 to 2.64, $p < 0.05$). Subgroup meta-analysis of b -value ≥ 500 (b) and b -value < 500 (c) was used for ADC calculation. ADC value difference was more pronounced in the group of b -value < 500 ($SMD = 2.31$, 95% CI 1.02 to 3.60 $p < 0.05$) than in the group of b -value ≥ 500 ($SMD = 1.38$, 95% CI 0.18 to 2.59 $p < 0.05$).

According to imaging mechanism, diffusion-weighted images are obtained by acquiring T2W images with the addition of diffusion-weighting gradient known as the “*b*-value”, which represents

Figure 3. Publication bias was not present ($t=1.51$, $p=0.162$).

diffusion gradient strength, duration of the gradient and interval between diffusion gradients.²⁶ This lowering of ADC in response to a larger maximal *b*-value is a fundamental property of DWI because of the impact on ADC not just of true molecular diffusion but of any source of incoherent motion. In particular, capillary perfusion is a source of perceived diffusion at lower *b*-values that artifactually elevates ADC value.²⁷ In our current study, we found ADC value difference of malignant and benign vertebral compression fractures was more pronounced in the group of *b*-value < 500 than in the group of *b*-value ≥ 500 . Therefore, *b*-value < 500 was more a valuable parameter than *b*-value ≥ 500 for discriminating malignant from benign vertebral compression fractures.

Heterogeneity is a potential problem when interpreting the results of all meta-analyses.²⁶ In this meta-analysis, we did find significant heterogeneity between studies. And studies were stratified by patient population to explore potential sources. Ethnicity-stratified analysis demonstrated higher ADC values in benign vertebral compression fractures in comparison to malignant tissues in both

the Asian and Caucasian subgroups. ADC value difference was more pronounced in the Asian subgroup. In addition, the benign group consisted of 312 vertebral fractures. The benign vertebral fractures included osteoporosis ($n = 65$), trauma ($n = 30$), infection ($n = 41$), osteoporosis or trauma ($n = 117$) and osteoporosis or trauma or infection ($n = 59$). The diffusion characteristics of the benign vertebral fractures such as osteoporosis, trauma and infection have rarely been investigated separately. Publication bias was not present in our current study.^{28,29}

Conventional MR techniques are the imaging test of choice in the diagnosis of pathological fractures. However, conventional MR is very sensitive but not always specific.¹⁵ Bone single photon emission CT may be comparable with MRI for differentiating malignant from benign vertebral fractures.³⁰ Discrimination based on the signal intensity ratio (SIR) of opposed-phase/in-phase was reported to be useful for differential diagnosis between malignant and benign vertebral compression fracture.³¹ High cellularity in tumour tissue yields lower ADC values than oedematous marrow in benign fractures.⁴ However, our study was not designed to explore the accuracy of ADC in the differentiation of benign and malignant vertebral fractures, since our data were not available to fill out cross-tabs in order to assess true positive (TP), true negative (TN), false positive (FP) and false negative (FN) cases.

There were several limitations to our study. Firstly, variable diffusion-weighting techniques were utilized among studies, such as steady-state free precession (which lacks the ability to absolutely quantify diffusion, thus not accounting for T2 shine-through), fast spin echo, line scan and echo planar imaging, as well as inconsistent diffusion pulse length.^{1,32} Secondly, interestingly, the mean ADC values varied significantly between study groups.^{1,32} The standardization of the acquisition protocol for diffusion-weighted imaging across the multicentre studies should be performed to further validate our results. Thirdly, our study was not designed to explore the accuracy of the ADC in the differentiation of benign and malignant vertebral fractures. Further studies with a larger sample size to determine the sensitivity, specificity, positive- and negative-predictive values of ADC in this aspect would certainly be useful.⁴ Fourthly, the diffusion characteristics of the benign vertebral fractures such as osteoporosis, trauma and infection have not been fully investigated separately.

In conclusion, even though the literature has been inconsistent, ADC value appears to be a reliable method to differentiate benign from malignant fractures. Low- b -value DWI was a more valuable parameter than standard- b -value DWI for discriminating malignant from benign vertebral compression fractures. Therefore, the use of low- b -value DWI for differentiation of benign and malignant vertebral fractures is recommended.

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