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Diffusion-weighted magnetic resonance imaging in differentiation between different vertebral lesions using ADC mapping as a quantitative assessment tool

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Abstract

Background: Diffusion-weighted imaging is one of the most useful clinical MRI techniques. Including this technique with other sequences used for routine spine scanning improves sensitivity and the capacity to characterize lesions. This study aims to evaluate the utility of apparent diffusion coefficient obtained from diffusion-weighted MR imaging in differentiating between benign and malignant vertebral lesions according to the optimal cutoff ADC value.

Results: This study included 30 patients at Ain Shams University hospitals; all of them were subjected to full clinical assessment and magnetic resonance imaging. Patients were classified into 4 groups: inflammatory lesions (12 cases) followed by malignant lesions (7 cases), then benign neoplastic lesions (6 cases), then traumatic lesions (3 cases) and osteoporosis (two cases). Inflammatory lesions revealed restricted diffusion. Benign neoplastic lesions/hemangioma showed low signal at DWIs due to free diffusion, while malignant/metastatic lesions showed restricted diffusion. Traumatic lesions showed restricted diffusion. The osteoporotic lesions showed iso- to hyper-intense signal at DWIs. The mean ADC value of the benign lesions was 1.8 ± 0.43 mm^2/s, while metastatic tumors was $0.96 \pm 0.5 \times 10^{-3}$ mm^2/s; however, overlapping values may be present.

Conclusions: Compared with benign tumors, malignant tumors have lower ADC values; nevertheless, some lesions, such as tuberculosis, have low ADC values that are like those of malignant tumors. Diffusion MRI and ADC values should always be analyzed in conjunction with standard MRI sequences as well as a thorough clinical history and examination.

Background

Metastatic bone disease is a well-known comorbidity in the progression of cancer. The occurrence of metastases has a significant impact on the management of oncological patients, as cancer cure is no longer conceivable after bone metastases have formed, and palliative therapy is the only viable option [1].

The commonest site of bone metastases is the vertebral bone marrow. The consequences are often significant morbidity and reduction in quality of life. In some cases, vertebral metastases do not cause symptoms. They often origin severe pain or reduction of mobility due to compression of the spinal cord by a direct mechanism or, indirectly, by causing a vertebral pathologic fracture [2].

In this scenario, the identification of spinal bone marrow abnormalities is critical for the treatment of oncological patients. Magnetic resonance (MR) imaging plays a crucial role in differentiation between benign and malignant spinal bone marrow disorders. However,

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morphological MR sequences might fail in differentiating between malignant and benign lesion because signal characteristics may overlap. Functional magnetic resonance imaging (fMRI) based on diffusion-weighted imaging (DWI) and derived apparent diffusion coefficient (ADC) maps can assist to clarify the type of a lesion by providing both qualitative and quantitative information on the tissue under study [2].

DWI emerges as a fast MRI sequence that allows for the examination of many types of vertebral and discal lesions in the spine without the use of contrast medium [3].

The mechanism of DWI depends essentially on the microstructure of a tissue which determine the Brownian motion of the water molecules. With a proportionate relationship, signal attenuation reflects the degree of water motion. The ADC value is calculated using maps derived via diffusional signal attenuation and allows for the quantification of Brownian motion. Concisely, tissues with a high free water component, such as those with low membrane and intracellular organelle content or high free extracellular water content, have lower DWI signal intensity and higher ADC signal intensity. In contrast, tissues with limited extracellular water content, such as tumors with strong cellularity, have higher signal intensity on DWI and isohypointensity on ADC maps [2].

Previous studies [4–6] have proposed diffusion-weighted imaging (DWI) as a suitable method for differentiating between benign and malignant marrow pathologies. However, simple qualitative DWI data analyses raise the question of whether the T2 shine-through effect may have contributed to the appearance of such images [7].

Because of this limitation, some investigators have quantified the diffusion in abnormal vertebrae based on the apparent diffusion coefficient (ADC) value and concluded that quantitative assessment is more useful than qualitative assessment in differentiating benign from malignant vertebral BMLs [8, 9].

Aim of the work

To evaluate the utility of apparent diffusion coefficient obtained from diffusion-weighted MR imaging in differentiating between benign and malignant vertebral lesions and to estimate the sensitivity and the specificity in differentiating benign and malignant vertebral lesions according to the optimal cutoff ADC value.

Methods

This prospective study was conducted at Ain Shams University hospitals during a period of 24 months. The study included 30 adult patients from both genders presented with vertebral abnormality in one or more vertebral bodies on conventional X rays, CT or MRI studies.

Sample size calculation was done using PASS 11 program for sample size calculation, setting power at 80% and alpha error at 0.05. The sample size of 30 lesions needed to detect sensitivity of 95% and specificity of 92%.

Patients with dense sclerotic vertebrae or having contraindications for MRI (as patients with cardiac pacemaker, any metallic stent, claustrophobia and morbid obesity) were excluded from the study.

Ethical considerations

The study group was informed about the nature and the purpose of the study. The study group was not exposed to any harm or risk and confidentiality was assured.

Study procedures

Patients underwent the following procedures: complete medical history, plain X-ray of the spine and magnetic resonance imaging (MRI) of the vertebral column using a 1.5 Tesla MRI scanner and multi-section fast spin echo pulse sequences with different repetition times (TR) and echo delay times (TE) to obtain T1 and T2 WI, intravenous contrast media administration in some patients, and histopathological correlation as well as clinical follow-up as the gold standard to classify the lesions as benign and malignant.

Patient preparation

There is a brief explanation of the examination (e.g., the need to lie motionless throughout the examination and the contraindication of presence of metallic objects, cardiac pacemaker, artificial cardiac valves or ferromagnetic nail emplacement or spinal fixation).

The patients were ordered to dress in medical gowns and to get any metallic objects apart, such as hair pins and coins ear rings, and then, the procedure was explained to the patient for reassurance and the patient was informed about the length of the examination and the knocking sounds which are usually heard during the examination and the value of remaining motionless. eGFR was checked in case of IV gadolinium administration (not to be administrated if less than < 30 mL/min/1.73 m^2).

- Patient positioning

  All MR examinations were performed with the patient supine and immobilized in a comfortable position with a CTL 8 channels coil (cervico-thoracic-lumbar coil) placed directly posterior to the region of interest (ROI). To decrease breathing arti-

facts, an elastic body belt was fastened around the upper abdomen. There was no respiratory triggering.

- Pulse sequences and scanning planes
  - T1 WIs (T1-weighted spin echo images): 2D scan mode and FSE (fast spin echo) sequences with repetition time (TR): 400–500 ms, echo time (TE): 15–25 ms, 20–25 cm field of vision (FOV) and 4 mm slice thickness. The number of axial slices was determined by the number and size of lesions. With the employment of the high-resolution phased array synergy surface coil, the number of excitations (NEX) is reduced to 3–5 excitations, resulting in a shorter scan duration.
  - T2 WIs (T2-weighted spin echo images): 2D scan mode and FSE sequences with TR: 3500–5000 ms, TE: 100–130 ms. FOV: 20–25 cm, slice thickness: 4 mm. Slice gap: 1–2 mm. Number of axial slices: variable according to the number and size of lesions. Acquisition time: 2.5 min. with the use of phased array coil.
  - Diffusion-weighted imaging and apparent diffusion coefficient mapping: DWMRI was performed for all patients. Using spin echo-planar imaging sequence, data were received in sagittal acquisition with 12,000/95/2200 ms for TR/TE/TI, respectively, 800 and 1000 s/mm2 b values, 24 ·40 cm FOV, 128 ·256 pixels matrix size, 5 mm slice thickness and 2.5 mm section gap. An ADC map was obtained.
  - Gd-DTPA (Magnivest) administration by means of intravenous injection at a dose of 0.1 mmol/Kg.body weight which is equivalent to 0.2 ml/kg. Body weight. After injection of Gd-DTPA, then short TR/TE images (T1 WIs) in at least two orthogonal planes were obtained. We must obtain both sagittal and axial T1 WIs before and after contrast injection to ensure precise comparison between the same region of interest. We must complete the post-injection images within the first 20 min following I.V. contrast injection.

Statistical methods

Analysis of data was performed using software MedCalc v. 19. Description of variables was presented as follows:

- Description of quantitative variables was in the form of mean, standard deviation (SD), minimum and maximum.
- Description of qualitative variables was in the form of numbers (No.) and percent (%).

Data were explored for normality using Kolmogorov–Smirnov test of normality. The results of Kolmogorov–Smirnov test indicated that most of data were normally distributed (parametric data), so parametric tests were used for most of the comparisons. The significance of the results was considered with P value ≤ 0.05.

Results

- The present study was carried out on 30 patients suspected clinically to have acquired spinal lesions. They were referred to radio diagnosis and imaging department from neurosurgery, neurology and orthopedic departments for MRI examination.
- The study group included 19 males (63.3%) and 11 females (36.6%) with mean age 48.9 ± 8.8 and range from 37 to 70 years (Table 1).
- Regarding diagnosis, 20% of cases had hemangioma, 23.3% metastases, 6.7% osteoporosis, 3.3% postoperative spondylodiscitis, 30% pyogenic spondylodiscitis, 6.7% T.B spondylodiscitis and 10% traumatic fracture (Table 2).
- Regarding relation between diagnosis and MRI signals, hemangioma was significantly associated with bright T1 signal and low DWI (100%) ($P. \leq 0.05$). Metastases were significantly associated with low T1 signal (100%), heterogeneous T2 (85.7%), T1 post-contrast enhancement (71.4%), bright DWI (100%) and lower ADC (0.95 ± 0.55) ($P. \leq 0.05$). Osteoporosis was significantly associated with bright T2 signal (100%) and iso- to hyper-intense DWI (50%) ($P. \leq 0.05$). Postoperative spondylodiscitis was significantly associated with low T1 signal, bright T2, T1 post-contrast enhancement (71.4%) and iso- to hypo-intense DWI (100%) ($P. \leq 0.05$).

Table 1 Diagnosis of the study group

Diagnosis	Study group ($n = 30$)	
	N	%
Hemangioma	6	20
Metastases	7	23.3
Breast cancer	3	10
Bronchogenic carcinoma	2	6.7
Hepatic sarcoma	1	3.3
Thyroid cancer	1	3.3
Osteoporosis	2	6.7
Postoperative spondylodiscitis	1	3.3
Pyogenic spondylodiscitis	9	30
T.B spondylodiscitis	2	6.7
Traumatic fracture	3	10

Table 2 MRI signals according to diagnosis in the study group

MRI	Diagnosis						
	Hemangioma (*n* = 6)	**Metastases (*n* = 7)**	**Osteoporosis (*n* = 2)**	**P.O spond. (*n* = 1)**	**Pyogenic (*n* = 9)**	**TB (*n* = 2)**	**Trauma (*n* = 3)**
T1 signal							
Low	0	7 (100%)	1 (50%)	1(100%)	8 (88.9%)	1 (50%)	3 (100%)
Bright	6 (100%)	0	1 (50%)	0	0	0	0
Low with eroded end	0	0	0	0	1 (11.1%)	1 (50%)	0
P .value	0.0250*						
T2 signal							
Bright	3 (50%)	1 (14.3%)	2 (100%)	1 (100%)	0	0	0
Heterogeneous	0	6 (85.7%)	0	0	9 (100%)	2 (100%)	3 (100%)
Intermediate	3 (50%)	0	0	0	0	0	0
P .value	0.0023*						
Contrast injection							
Cases with contrast	0	5 (71.4%)	0	1 (100%)	8 (88.9%)	2 (100%)	0
Cases without contrast	6 (100%)	2 (28.6%)	2 (100%)	0	1 (11.1%)	0	3 (100%)
T1 enhancement							
Simple	0	3 (42.9%)	0	1 (100%)	1 (11.1%)	0	0
Epidural collection	0	2 (28.6%)	0	0	7 (77.8%)	0	0
Para spinal collection	0	0	0	0	0	1 (50%)	0
Epidural and para spinal	0	0	0	0	0	1 (50%)	0
P .value	< 0.0001*						
DWI signal							
Bright	0	7 (100%)	0	0	9 (100%)	2 (100%)	3 (100%)
Low	6 (100%)	0	1 (50%)	0	0	0	0
Iso- to hyperintense	0	0	1 (50%)	0	0	0	0
Iso- to hypointense	0	0	0	1 (100%)	0	0	0
P .value	0.0001*						
ADC							
Mean	1.81	0.96	2.10	2.00	1.84	0.65	2.16
SD	0.07	0.55	0.42	0.00	0.26	0.070	0.057
P value	< 0.001*						

**P* ≤ 0.05 is considered significant

Pyogenic spondylodiscitis was significantly associated with low T1 signal (88.9%), heterogeneous T2 (100%), T1 post-contrast enhancement (88.9%) with epidural collection (77.8%) and bright DWI (100%) ($P. \leq 0.05$). T.B spondylodiscitis was significantly associated with low T1 signal with eroded endplate (50%), heterogeneous T2 (100%), T1 post-contrast enhancement (100%) with epidural and paraspinal collection (50%), bright DWI (100%) and lowest ADC (0.65 ± 0.070) ($P. \leq 0.05$). Traumatic fracture was significantly associated with low T1 signal (100%), heterogeneous T2 (100%), bright DWI (100%) and highest ADC (2.16 ± 0.057) ($P. \leq 0.05$).

- The mean ADC value of the benign lesions (benign neoplasm, trauma, infection and osteoporosis) was 1.8 ± 0.43 mm^2/s, while metastatic tumors was $0.96 \pm 0.5 \times 10^{-3}$ mm^2/s; however, overlapping values may be present. The mean ADC of tuberculous

spondylitis was 0.65 × 10^{-3} mm^2/s, which was similar to that of malignant acute vertebral fractures.

- Thus, apparent diffusion coefficient (ADC) was significantly higher in cases with benign lesion than cases with malignant lesion (*P.* < 0.001) (Table 3).
- Apparent diffusion coefficient (ADC) had significant predictive value for diagnosis of malignant lesion at cutoff level ≤ 0.9 × 103, with sensitivity 85.7% and specificity 91.3% and benign lesion at cutoff level > 0.9 × 103, with sensitivity 91.3% and specificity 85.7% (*P.* < 0.05).

Discussion

MRI has rapidly become the modality of choice for imaging musculoskeletal disorders in recent years. Although MRI is extremely sensitive for detecting bone marrow lesions, enhancing specificity requires a thorough understanding of normal and abnormal marrow morphology as well as creative acquisition sequences [10].

DWI is mainly based the Brownian movement of water molecules according to a Gaussian distribution. It is a noninvasive imaging approach that uses the random, translational motion of water protons in a biologic tissue to indicate tissue-specific diffusion capability and can be utilized for tissue characterization. So, diffusion-weighted MR sequences add microscopic information in addition to the macroscopic data obtained by standard sequences [11].

The number of diffusion barriers, such as membranes, tight junctions, fibers, macromolecules and cell organelles, indirectly determines the diffusion capacity [12].

According to Fawzy et al. [11] and Karchevsky et al. [13], the number of diffusion barriers increases in quickly growing tissues with high energy turnover, such as tumor tissue, resulting in restricted diffusion and a loss in diffusion capacity. According to this theory, the tumor tissue's mobility of water protons is restricted, resulting in higher signal intensities on DWI due to its low diffusion capacity. As a result, malignancy looks hyperintense on DWI, whereas benign tissues and liquids appear hypointense.

T1 and T2 traces may potentially play a role in the DWI signals assuming diffusion restriction and, as a result, malignancy. These are known as "shine through effects," and they can be avoided by using diffusion gradients with b-factors greater than 150 s/mm^2 and quantitative DWI analysis, which can be accomplished by calculating the apparent diffusion coefficient (ADC), which is thought to reflect tissue-specific diffusion capacity and is an objective parameter for tissue characterization [14].

In this study, we revealed that visual assessment of high signal intensity on a high b-value (800) was not specific for malignancy because acute benign fractures, inflammation and hyperactive hematopoietic marrow can all cause similar diffusion restriction, which agrees with Zidan et al. [15]; Koh et al. [16]; Ballon et al. [17].

Zhou et al. [18] and Castillo et al. [19] noted that diffusion-weighted image signal intensity characteristics are highly nonspecific; hyperintense, isointense or hypointense signal was observed for both benign lesions and metastases. Our study also reported that 74% of benign lesions were of high signal on DWIs and 26% were of low signal, while the malignant lesions, 100%, were of high signal on DWIs (Fig. 1).

On the other hand, the quantitative assessment by measuring the ADC value was able to distinguish benign from malignant high signal intensity on DWI. This was in agreement with Leeds et al. [20]; Zhou et al. [18]; Padhani et al. [21]; Zidan et al. [15], who highlighted the necessity of correlating high b-value DW images with corresponding ADC values (Fig. 2).

Dietrich et al. [22] stated that the majority of the studies found ADCs of normal vertebral bone marrow in a range between 0.2 and 0.6 × $10^{-3}$$mm^2$/s. The comparably large variations of the presented results may be explained by experimental differences including different pulse sequences**.** Our study reported that the mean ADC value of normal vertebrae was about 0.51 ± 0.017 × 10^{-3} mm^2/s, and this was in agreement with several studies that defined similar ADC values of normal vertebral bone marrow; Fawzy et al. [11]: 0.31 ± 0.11 × 10^{-3} mm^2/s, Dietrich et al. [22], 0.42 ± 0.14 × 10^{-3} mm^2/s, and 0.37 ± 0.33 × 10^{-3} mm^2/s.

Table 3 Predictive value of ADC for diagnosis of malignancy by receiver operating characteristic curve (ROC)

Diagnosis	ADC						
	AUC	Cutoff	Sens%	Spec%	PPV	NPV	*P* value
Malignant	0.807	≤ 0.9 × 10^3	85.7	91.3	75.0	95.5	0.0108*
Benign	0.807	> 0.9 × 10^3	91.3	85.7	95.5	75.0	0.0108*

AUC area under curve, *Sens* sensitivity, *Spec* specificity, *PPV* positive predictive value, *NPV* negative predictive value

**P* ≤ 0.05 is considered significant

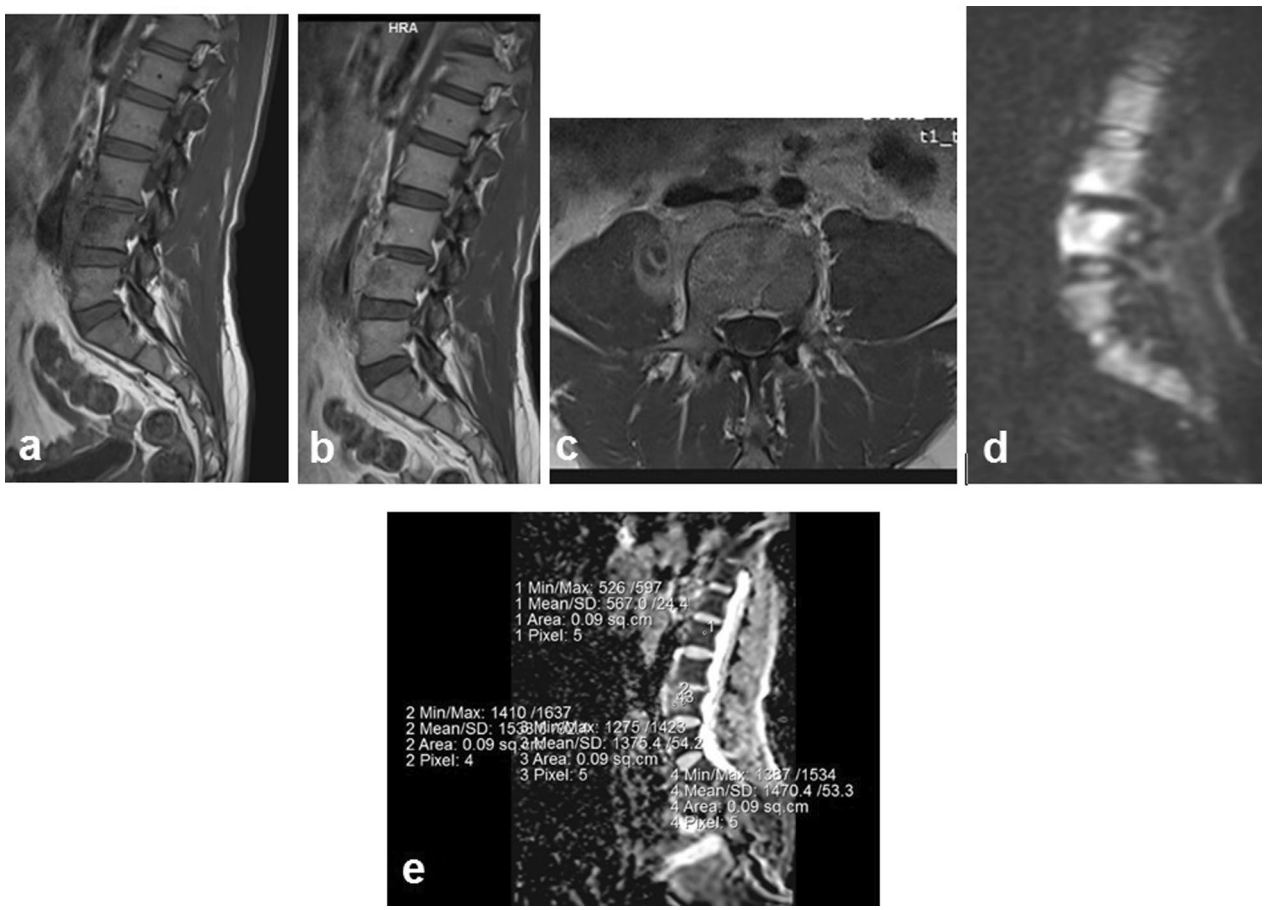

Fig. 1 **a**–**e** A 42-year-old male patient with L3-4 pyogenic spondylodiscitis. Sagittal T1 (**a**) shows L3-4 opposing end plates bone marrow edema. Sagittal T1 post-contrast (**b**) and axial T1 post-contrast (**c**) show L3-4 bone marrow, opposing end plates enhancement with prevertebral and right paravertebral enhanced soft tissue component. Sagittal DWI (**d**), ADC (**e**). DWI demonstrates diffusion restriction with bright signal intensity, while ADC shows bright signal with mean value about 1.4–1.5 × 10^{-3} mm^2/s

Zidan et al. [15] stated that normal yellow marrow had the lowest ADC value and the infiltrated neoplastic marrow as well as hypercellular red marrow had higher ADC value, and on the other hand, the infective/inflammatory bone marrow lesion had the highest ADC value. This was in agreement with our study.

Thus, it was concluded in agreement with Zidan et al. [15] that ADC values of malignant marrow are not overlapping with the following benign bone marrow lesions: acute fracture, osteoporosis, inflammatory pyogenic marrow lesions and normal yellow marrow, but the ADC values between malignant and TB inflammatory/ infective lesions were overlapping (Fig. 3).

In our study, ADC had significant predictive value for diagnosis of malignant lesions at cutoff value $\leq 0.9 \times 10^{-3}$, with sensitivity 85.7% and specificity 91.3%, almost similar to Pozzi et al. [23] study which stated 0.952×10^{-3} as an optimal cutoff mADC value with 81.3% sensitivity and 55% specificity.

Mohson et al. [24] study showed a sensitivity of 94% and a specificity of 95%, and this is highly comparable to our study.

Neubauer et al., [25], Pekcevik et al. [26] and Ginat et al. [27] declared that mADC values of 1.03×10^{-3} mm^2/s, 1.37×10^{-3} mm^2/s and 1.01×10^{-3} mm^2/s, respectively, are reliable cutoff values to identify malignant musculoskeletal tumors.

Regarding the PPV and NPV of ADC value in detection of vertebral marrow lesions secondary were 75% and 95% compared to 89% and 97% in a study done by Mohson et al. [24].

Some limitations should be considered. Our study included a wide spectrum of tumors, so some histotypes could not be represented, making it difficult to understand the actual link between the different spinal

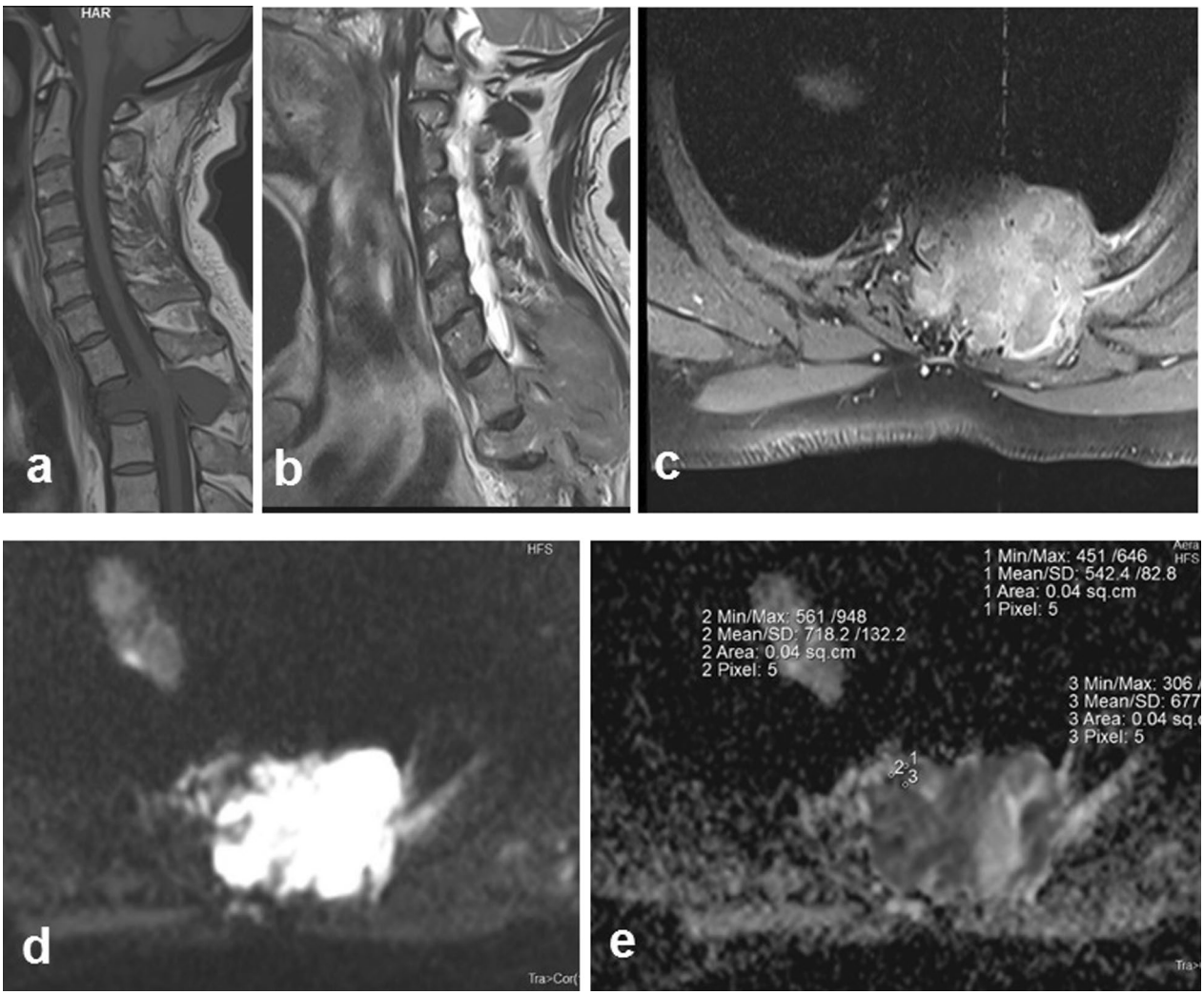

Fig. 2 A 64-year-old man with metastatic hepatic sarcoma. Sagittal T1 (**a**) and T2 (**b**) images show the partially collapsed D2 with metastatic lesion and large left sided extra-osseous soft tissue component, being, respectively, hypo- and iso-intense with respect to the surrounding tissue. Post-contrast axial T1 (**c**) shows homogenous post-contrast enhancement. The corresponding axial DWI image (**d**) demonstrates bright signal denoting restricted diffusion that shows on ADC map (**e**), mean value of 0.6–0.7 × 10^{-3} mm^2/s

tumors and their ADC values. Further studies using a narrower spectrum of tumor types should be performed to better understand the role of DWI in the differential diagnosis of bone tumors. Furthermore, it has been shown that residual fat signal may determine a possible underestimation of ADC values, especially in bone marrow, where there are large proton density fat fraction values [28]. This may have affected our measurements on both normal bone marrow and tumors. Last, the FOV used to obtain DWI sequences was the same as the standard MR protocol, whereas a DWI sequence with a smaller field of view may lead to a more accurate ROI placement [29].

Spinal lesion differential diagnosis remains challenging even in MRI, and recently some studies stated that MRI radiomics combined with machine learning may be useful in spinal lesion assessment [30].

Conclusions

Standard T1W, T2W and fat suppression sequences in conventional MRI cannot distinguish between benign and malignant vertebral marrow lesions. DWI can help with the characterization and differential diagnosis of

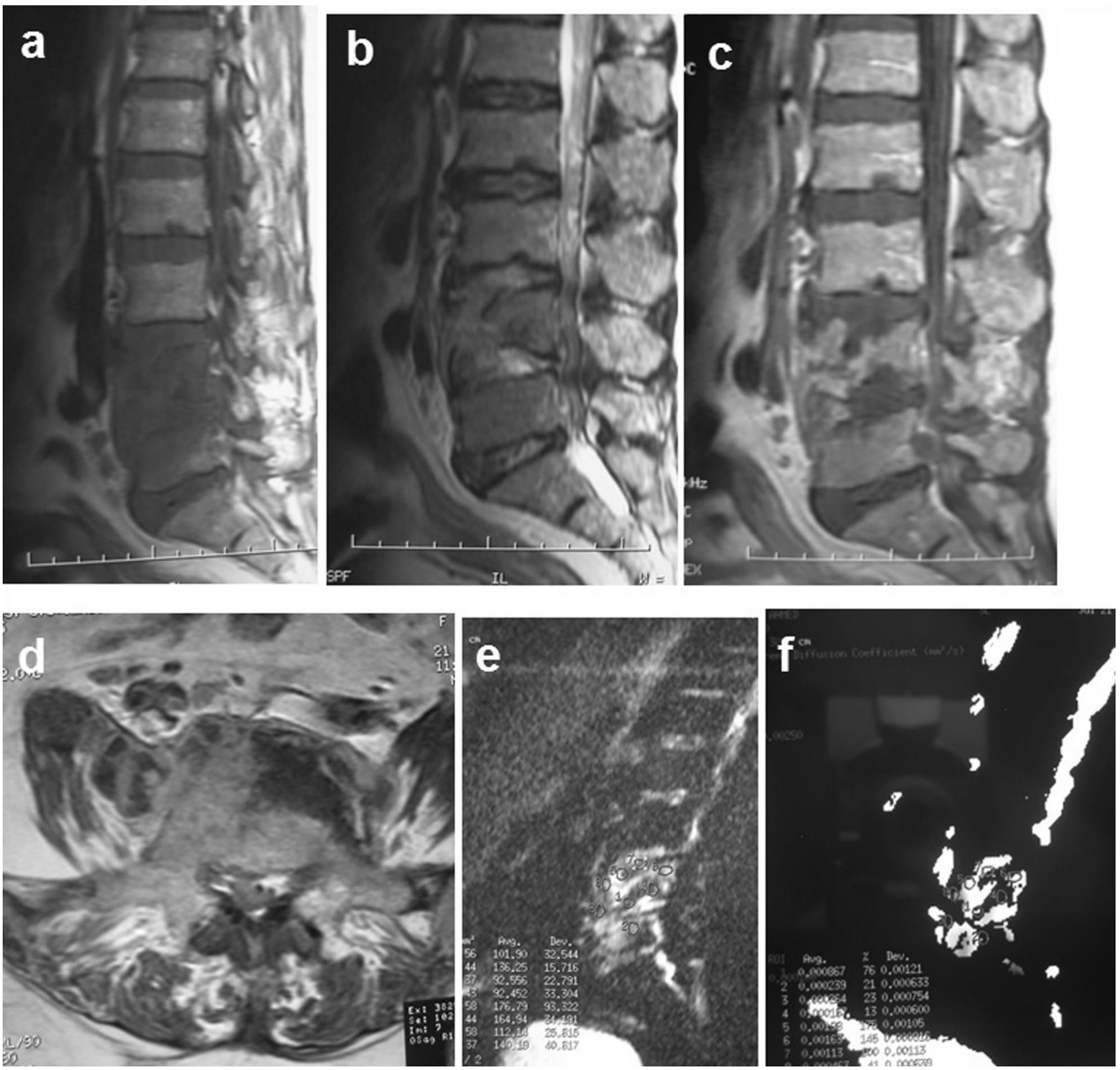

Fig. 3 A 47-year-old woman with L4 wedging (TB spondylodiscitis). Sagittal T1 (**a**) and T2 (**b**) images show the L4 wedging, eroded end plates with diffuse bone marrow low signal at T1 images and bright T2 signal of L4-5 disc. Post-contrast sagittal T1 (**c**) and axial T1 (**d**) show L4 bone marrow and L4-5 disk heterogeneous contrast enhancement with pre-, paravertebral collections and subtle epidural soft tissue component. Sagittal DWI image (**e**) shows bright signal that shows on ADC map (**f**), mean value of 0.6×10^{-3} mm^2/s

a variety of bone marrow diseases in the spine. Useful information can be obtained from quantitative ADC values in order to distinguish benign from malignant lesions. In general, malignant tumors have lower ADC values than benign lesions; however, some lesions, such as tuberculosis, have low ADC values that are similar to those of malignant lesions. So, diffusion MRI and ADC coefficient values should always be analyzed in conjunction with standard MRI sequences as well as a thorough clinical history and examination.

Abbreviations

ADC: Apparent diffusion coefficient; DWI: Diffusion-weighted imaging; fMRI: Functional magnetic resonance imaging; FOV: Field of view; NEX: Number of excitations; ROC: Characteristic curve; ROI: Region of interest; TB: Tuberculosis; TE: Echo time; TR: Repetition time.

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Authors contributions
KEA and YIA gave the idea. HGM put study design. MAE collected the patients data and analyzed them as well as wrote the paper with revision. They all approved the final version of the manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Research Ethics Committee of the Faculty of Medicine at Ain Shams University in Egypt on 18 September 2019; reference number of approval: 294/2019. All patients included in this study gave written informed consent to participate in this research.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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