Diagnostic Value of WB-DWI Versus 18 F-FDG PET/CT for the Detection of Multiple Myeloma

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Abstract

BACKGROUND Whole body diffusion weighted imaging (WB-DWI) is commonly used for the detection of multiple myeloma (MM). Comparative data on the efficiency of WB-DWI compared with 18 F positron emission tomography computed tomography (18 F-FDG PET/CT) to detect MM are lacking.

METHODS This was a retrospective, single-center study of twenty-two patients with MM enrolled from January 2019 to December 2019. All patients underwent WB-DWI and 18 F-FDG PET/CT. Pathological and clinical manifestations as well as radiologic follow-up were used for diagnosis. The overall accuracy, sensitivity, specificity, positive predictive value and negative predictive value of both methods were compared. The appearance diffusion coefficient (ADC) values of MM lesions and false-positive lesions were estimated.

RESULTS A total of 214 MM bone lesions were evaluated. WB-DWI showed a higher overall accuracy than PET/CT (75.7% and 55.6%, respectively; < 0.05). However, for sensitivity, specificity, positive predictive value and negative predictive value, there were no significant differences for WB-DWI vs PET/CT (99.3% and 83.9%, 64.9% and 94.8%, 63.6% and 54.2%, 98.1% and 65.3%, respectively). The ADC value for MM lesions was significantly lower than that for false-positive lesions ($p < 0.001$). Receiver operating curve (ROC) curve analysis showed that the AUC was 0.846, and when the cut-off value was 0.745×10 -3 mm 2 /s, the sensitivity and specificity were 86.0% and 82.4%, respectively, which distinguished MM lesions from non-MM lesions.

CONCLUSION WB-DWI may be a useful tool for the diagnosis of MM bone disease due to to higher overall accuracy and measurements of ADC values compared with PET/CT.

Background

MM is a malignant plasma cell proliferative disease characterized by the overproduction of monoclonal immunoglobulins or light chains[1], which invade the bone marrow and gradually replace normal cells.[2] Osteolytic disease is one of the main complications of MM.[3] The progression of intramedullary lesions needs in MM must be evaluated to determine staging and estimate potential treatment response.[4]

Whole body diffusion weighted imaging (WB-DWI) and 18 F positron emission tomography computed tomography (^{18}F-FDG PET/CT) are recommended in new clinical guidelines.[5, 6] The advent of PET has enabled medical imaging techniques to assess cellular metabolic activity in living tissues.[4, 7] Because of the limitations of fluorodeoxyglucose (FDG) tracer technology, the specificity of PET/CT in detecting MM intramedullary lesions, especially diffuse invasive lesions, is suboptimal.[8] At the same time, magnetic resonance (MR), a routine examination method, shows ideal sensitivity for the detection of MM bone disease.[9] WB-DWI does not only detect the movement of water molecules, but also has a large imaging range and no radiation.[10] WB-DWI diagnosis results may be related to disease burden and treatment response.[11]

Both WB-DWI and ^{18}F-FDG PET/CT have been preliminarily applied in the diagnosis of MM bone disease. However, the comparative potential diagnostic value of the two methods has not been elucidated. Herein, we present comparative data on WB-DWI and ^{18}F-FDG PET/CT for the diagnosis of MM bone disease.

Subjects And Methods

This study was approved by the Ethics Committee of First Hospital of Jilin University. Written informed consent was obtained from all patients.

Subjects

A total of 22 patients who presented at the hospital between January 2018 and December 2019 (15 male and 7 female) were included. The mean age was 57.06 years old (range: 40–69 years). Eligible patients met the National Comprehensive Cancer Network (NCCN) diagnostic criteria for MM.[12] The inclusion criteria were as follows: 1) aged from 18–70 years; 2) diagnosis of MM in accordance with established diagnostic criteria; and 3) patients had to undergo our standard scanning protocol with WB-DWI and ^{18}F-FDG PET/CT. We excluded patients with bone diseases other than MM, and MM patients without bone lesions. Poor quality image data due to body movements or other artifacts were excluded.

The Type of bone disease included diffuse pattern (n = 8) and focal pattern (n = 13). Patients underwent WB-DWI and ^{18}F-FDG PET/CT before treatment without exception with a maximum interval of 1 week.

Gold standard: pathologic examinations or clinical/imaging follow-up data. All patients received stem cell transplantation following induction chemotherapy. Each patient received one of three chemotherapy treatments (VCD = bortezomib, cyclophosphamide and dexamethasone; VD = bortezomib and dexamethasone; VAD = vincristine, doxorubicin and dexamethasone) followed by mobilization chemotherapy with CAD (cyclophosphamide, doxorubicin and dexamethasone). Treatment response was assessed using the NCCN guidelines for MM.[12] Every patient experienced regular follow-up for at least 6 months. Each patient's follow-up program included comprehensive clinical assessment, laboratory results, and regular imageology examination. During follow up, nine patients underwent imaging by CT, and thirteen patients were followed up by conventional MR. Bone lesions were confirmed as related to MM by pathological examination; progression or improvement was monitored by imaging. Lesions that were not confirmed by pathology or those that did not change during follow-up were not treated as MM lesions.

WB-DWI

A 3.0 T Ingenia MR scanner was used to perform WB-DWI (Philips, The Netherlands) with a body coil. STIR and echo-planar DWI with STIR were conducted, and parameters were set as follows: 0 and 800 s/mm^2 of b value were adopted; repetition time (TR)/echo time (TE)/inversion time (TI),

5200/106/180 ms; image matrix, 128 × 128; field of view (FOV), 400 mm; number of excitations (NEX), 4; slice thickness/gap, 7/0 mm; number of slices, 24; and acquisition time, 4 min. Six to seven scans were conducted with a total scan time of close to 35 min. A contrast agent was not used. The generation of ADC maps was based on DWI images from an EWS workstation (Philips, The Netherlands).

PET/CT

An LS PET/CT scanner (Discovery, GE) was used to perform ^{18}F-FDG PET/CT. ^{18}F is produced by a Ministrace accelerator and ^{18}F-FDG is synthesized by a Tracer Lab positron drug synthesis system. Radiochemical purity is more than 95%. The patient should ensure that drugs that stimulate hematopoietic function are not used 2 weeks before the examination, and the barium test is not carried out within 1 week before the test. Strenuous physical labor should be avoided one week before examination. The patient should fast for more than 6 hours to ensure a blood glucose concentration of < 7.8 mmol/L before the examination. Intravenous injection ^{18}F-FDG should be performed according to body mass (4.4–5.5 MBq/kg). PET/CT was performed 50–70 minutes after injection of F-FDG, and the stomach cavity was filled with 500 ml of water 5 minutes before examination. Patients were instructed to lie on their backs on the examination bed with their upper limbs naturally placed on both sides of the body. The body position was fixed and the bones of both upper limbs were kept in the inspection field.

Firstly, spiral CT scans (tube voltage 140 kV, current 90 mA, layer thickness 4.5 mm) were performed. The scanning ranged from cranial top to middle femur. PET images were collected in the same range (7–8 beds, 2.5 min/bed). The ordered subset expectation maximization (OSEM) algorithm was adopted for image reconstruction. CT data were used to correct PET image attenuation, and the corrected images were merged with CT images.

Imaging Diagnosis

The whole skeleton was divided into 18 regions for analysis. These areas included the skull, sternum, bilateral clavicle, bilateral scapula, bilateral upper femur, bilateral ribs, cervical, thoracic and lumbar spine, sacral vertebra, bilateral ilium and upper femur. Since the distal bone of the extremities is not in the scope of PET/CT scans, these were excluded from the scope of observation.

Two radiologists with over 10 years' experience read and rechecked the WB-DWI information. Both reviewers were blinded to data other than clinical data. Bone disease was evaluated by DWI (b = 0 and 800 mm^2/s) as well as ADC maps. Hyperintense or isointense lesions on DWI (b = 1000 mm^2/s) and hypointense lesions on ADC maps were considered MM lesions. The region of interest (ROI) was automatically identified on ADC maps using appropriate software, including all slices of the lesion.

Two nuclear medicine doctors with over 10 years' experience analyzed the FDG-PET/CT images. Both reviewers were blinded to the results other than clinical data. Standard uptake was calculated through the

ROI on the suspected lesions and normal metabolic function of liver tissue (or blood pools of patients with liver diseases). When the uptake value of a given site was higher than that of the liver or blood pool, combined with morphology data, it was reasonable to regard such lesions as MM lesions.

ADC measurements on WB-DWI

Delineation of ROI and measurement of the ADC values were performed by a single attending radiologist. The software automatically outlined all lesions and layers showing lesions. Where the automatic sketch was not accurate, manual modification of the accurate contour of the lesion was required. For diffuse lesions, all the levels of the whole bone need were outlined. We generated ADC values for each lesion. There were 224 lesions from 22 patients overall. All measured slices included lesions. DWI data were processed and the ADC maps were generated using an EWS workstation (Philips, The Netherlands).

Statistical Methods

The Chi square test was used to detect overall accuracy, sensitivity, specificity, positive predictive value and negative predictive value of WB-DWI and FDG PET/CT. A t test was used to evaluate the difference in ADC value between negative findings and MM lesions. $p < 0.05$ was considered statistically significant. The ability of the ADC value to distinguish false-positive results from MM lesions required ROC curve and AUC analysis. SPSS (version 20.0, IBM) was used for statistical analysis.

Results

Clinical characteristics

There were 22 patients enrolled in this study. Table 1 shows their demographic and clinical characteristics at baseline. Men were more commonly affected by MM than women (N = 15 vs 7, respectively). The mean ADC value from all 224 bone lesions in all patients was calculated.

Findings following WB-DWI and FDG PET/CT imaging

A total of 136 MM lesions were confirmed using pathological data from tissue biopsies or follow-up data (116 bone regions, 22 patients). WB-DWI identified 162 lesions, with 27 false positives and one false negative. In contrast, FDG PET/CT diagnosed 119 lesions with four false-positives and 20 false negatives. Our results were consistent with the gold standard. WB-DWI scored more highly than PET/CT for overall accuracy (75.7% and 55.6%, respectively; $P < 0.05$), whereas there was no significant difference in the sensitivity, specificity, positive predictive value or negative predictive value between the two (99.3% and 83.9%, 64.9% and 94.8%, 63.6% and 54.2%, 98.1% and 65.3%, respectively; all $P > 0.05$) (Table 2). The overlap for misdiagnoses between both methods was three false-positives and one false-negative.

ADC value-based assessment of false-positive findings and discrimination of mm lesions by ROC Curve and AUC analyses

A total of 224 lesions covering 95 bone segments were used for the quantitation of ADC values in this study. There were 27 false-positive MM lesions overall.

WB-DWI detected 162 lesions altogether. According to the gold standard, 135 lesions were MM lesions and 27 were false positives. The ADC value of MM lesions was lower compared with false positives ($p < 0.05$, Table 3 and Fig. 1). The median ADC value of MM lesions was 0.678×10^{-3} mm ^{2} /s, and that of false positive was 0.979×10^{-3} mm ^{2} /s (interquartile range: 0.609–0.815×10^{-3} mm ^{2} /s and 0.902–1.003×10^{-3} mm ^{2} /s).

Using ROC curve and AUC analysis, ADC was used to distinguish false-positive results from true MM lesions (Fig. 2). The overall AUC was 0.846, and the ADC cut-off value to distinguish non lesions from MM bone disease was 0.745×10^{-3} mm^2/s, with a sensitivity and specificity of 86.3% and 83.4%, respectively.

Discussion

In this study, the comparative effectiveness of WB-DWI and FDG PET/CT for MM diagnosis was evaluated, and ADC values were applied for further exploration. Our results showed that the sensitivity and specificity of WB-DWI for detecting MM lesions in bone marrow was similar to that of FDG PET/CT. However, in terms of overall accuracy, WB-DWI was superior to PET-CT. The ADC value of bone areas positive for WB-DWI, FDG PET/CT and gold criteria was significantly lower than that for negative areas. The ADC value for distinguishing MM lesions from non-lesions showed that WB-DWI had higher specificity than FDG PET/CT. Therefore,

WB-DWI combined with the ADC value may play an important role in the quantitative and qualitative assessment of MM bone lesions.

A recent study indicated that different types of MM lead to variations in ADC values detected by WB-DWI imaging, and focal patterns are more easily affected by treatment than diffuse patterns and "salt and pepper" patterns.[13] Although treatment response was not evaluated in our study, different patterns in MM were analysed, including focal patterns and diffuse patterns. Importantly, when drawing ROI, all slices of all lesions were included.

Among many features of MM, bone disease is the most common; 90% of patients will experience bone disease[14], and osteolytic bone disease is most frequently observed.[15] WB-DWI and PET/CT have been increasingly used to evaluate MM bone disease. Some researchers have suggested that PET/CT is more sensitive for the accurate diagnosis of MM suspicious lesions[16–18], while others have found that the

sensitivity of conventional MR is superior to that of PET/CT. Importantly, the correlation between PET/CT results and patient management is stronger.[9] Studies have also shown that in the diagnosis of MM, standardized uptake value (SUV) should not be the only criteria used to evaluate prognosis.[19] WB-DWI is more sensitive for intramedullary lesions than PET/CT in all areas except the skull; however, the sensitivity in extramedullary lesions is similar (Fig. 3).[10] Although WB-DWI had no advantage over FDG PET/CT in terms of sensitivity for diagnosing MM lesions, the overall accuracy was higher than that of PET/CT. Therefore, we should try to apply WB-DWI more frequently to detect MM bone disease. This will not only lead to cost savings,[20] but would also provide a useful supplementary diagnostic tool to FDG PET/CT. However, in the present study, the comparison between FDG PET/CT and WB-DWI showed no obvious advantage in the sensitivity of MM bone disease detection.

Besides FDG PET/CT, WB-DWI is also important in MM research. Whole body magnetic resonance imaging (WB-MRI) combined with DWI may improve the diagnostic accuracy for MM patients with progressive disease (PD) up to 88.9%.[6] Research has confirmed that combining DWI images with standard MRI can improve the diagnosis efficiency of MM and help differential diagnosis.[21] It must also be noted that although WB-DWI is more sensitive than PET/CT (94% vs 75%, respectively) for diagnosis, specificity was less satisfactory than PET/CT (86% vs 43%, respectively).[22]

When the baseline ADC value of MM patients was 0.808×10^{-3} mm^2/s, the sensitivity and specificity of predicting response after treatment was 54.09% and 68.05%, respectively.[23] The ADC value is not only important for MM diagnosis, but also plays a role in monitoring treatment response. When the ADC increased by 78.0%, the specificity of predicting a deep response in MM treatment increased by 90.7%.[24] Previous research showed that the signal intensity of the short tau inversion recovery (STIR) sequence can be used to monitor treatment response in MM.[25] The ADC value is also important for other tumors including benign ovarian epithelial tumors. The ADC value was significantly higher than that of malignant ovarian epithelial tumors; the AUC of the ADC for differentiating benign and malignant tumors was shown to be 0.921.[26] However, in a study involving the differentiation of vertebral hemangioma from MM and other malignant bone focal deposits, when the ADC threshold was 0.872 and the AUC was 0.93, sensitivity was 84.7% and specificity was 91.8%.[27]

In recent years, studies of PET/CT and WB-DWI have highlighted multiple reasons behind the misdiagnosis of bone disease. FDG uptake is observed in numerous scenarios including inflammation[28], tuberculosis[29], severe fatty degeneration of bone marrow[30] and so on. WB-DWI and PET/CT were associated with the same difficulties in differentiating MM bone disease from non-lesions. The influence of fractures in DWI on the judgement of bone disease should be taken into account. There is also evidence that the ADC value of pelvic insufficiency fractures was significantly higher than that of bone metastasis in cervical cancer.[31] In this study, some of the enrolled patients had both MM bone disease and pathological fractures. These complex conditions need to be carefully observed in combination with the characteristics of signal and FDG uptake as detected by WB-DWI and FDG PET/CT.

Conclusions

Our results demonstrate the diagnostic value of WB-DWI in MM compared with ^{18}F-FDG PET/CT, and clarify the differential value of ADC values. This study may provide useful reference information for exploration of the application of WB-DWI in MM diagnosis.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

Bei Zhang collected the data of MM patients and wrote the manuscript. Li Zhang designed the MR-sequences and helped draft the manuscript. Bingyang Bian contributed to the study design and revised MR scan protocol. Zining Zhu and Fang Lin supervised the experimental process. Jiping Wang was responsible for designing the research plan. All authors have read the manuscript and approved the final version.

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Availability of data and materials

All analyzed data are included in this published article and its supplementary information file. The original data are available upon request to the corresponding author.

Ethics approval

The study was approved by the institutional review board, and personal informed written consent has been obtained.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Baseline demographics and clinical characteristics of the patient population

Parameters	Baseline demographics and clinical characteristics
No. of subjects	22
Sex (M/F)	15/7（68.2%/31.8%）
Age (mean) (yr)	57.06 ± 9.72
No. of lesions	214
Mean ADC value ($\times 10^{-3}$ mm^2/s)	0.703(0.611-0.908)

Table 2

Parameters	PDG PET/CT	WB-DWI	p
Overall accuracy	55.6%	75.7%	0.001
Sensitivity	83.9%	99.3%	0.05
Specificity	94.8%	64.9%	0.05
PPV	54.2%	63.6%	0.05
NPV	65.3%	98.1%	0.05

PPV= positive predictive value, NPV=negative predictive value.

Table 3 Within-subjects ADC value of MM lesions and non

Classification	ADC value of MM lesion ($\times 10^{-3}$ mm^2/s)	ADC value of false positive lesion ($\times 10^{-3}$ mm^2/s)	p value
WB-DWI	0.678 (0.609 - 0.815)	0.979 (0.902 – 1.003)	0.05*

* Significant difference

Figures

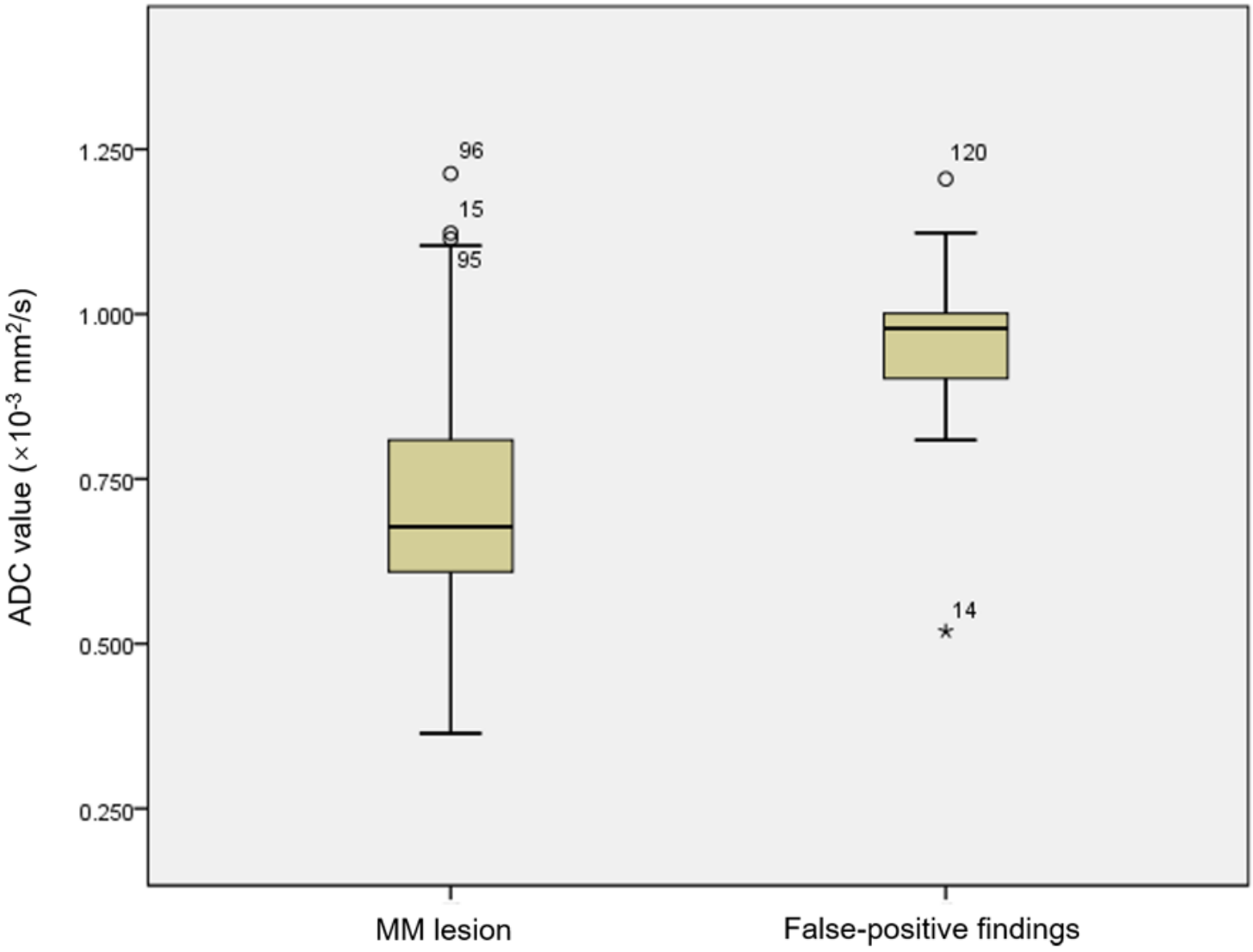

Figure 1

Box-and-whisker plot of differences in ADC values between multiple myeloma (MM) lesions and false-positive results, detected by WB-DWI.

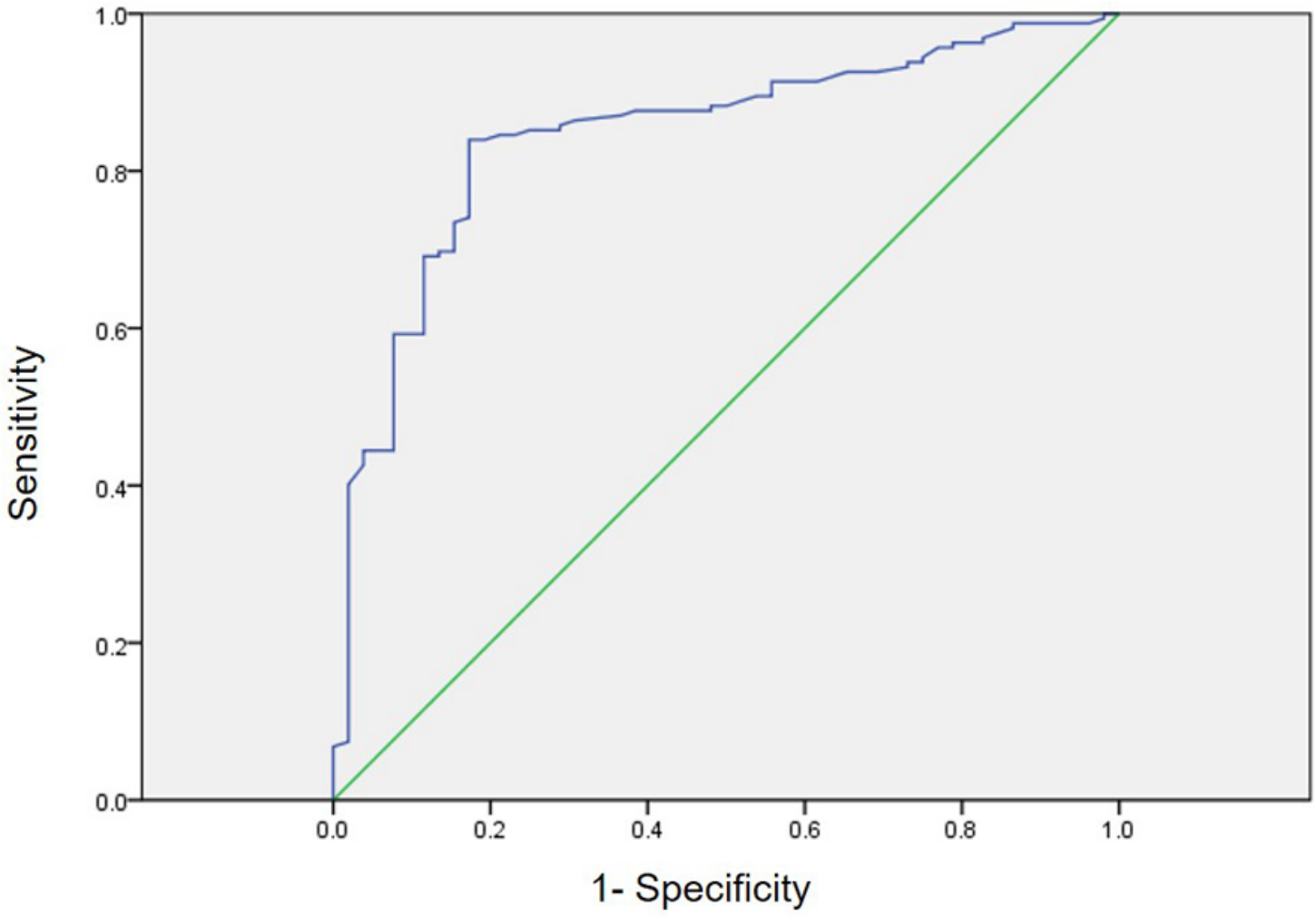

Figure 2

ADC values based on ROC curve analysis, which was used to distinguish multiple myeloma (MM) lesions (false-positive results) from non-MM lesions. The AUC was 0.846 and the ADC cut-off value was 0.745×10-3 mm2/s; $p < 0.001$.

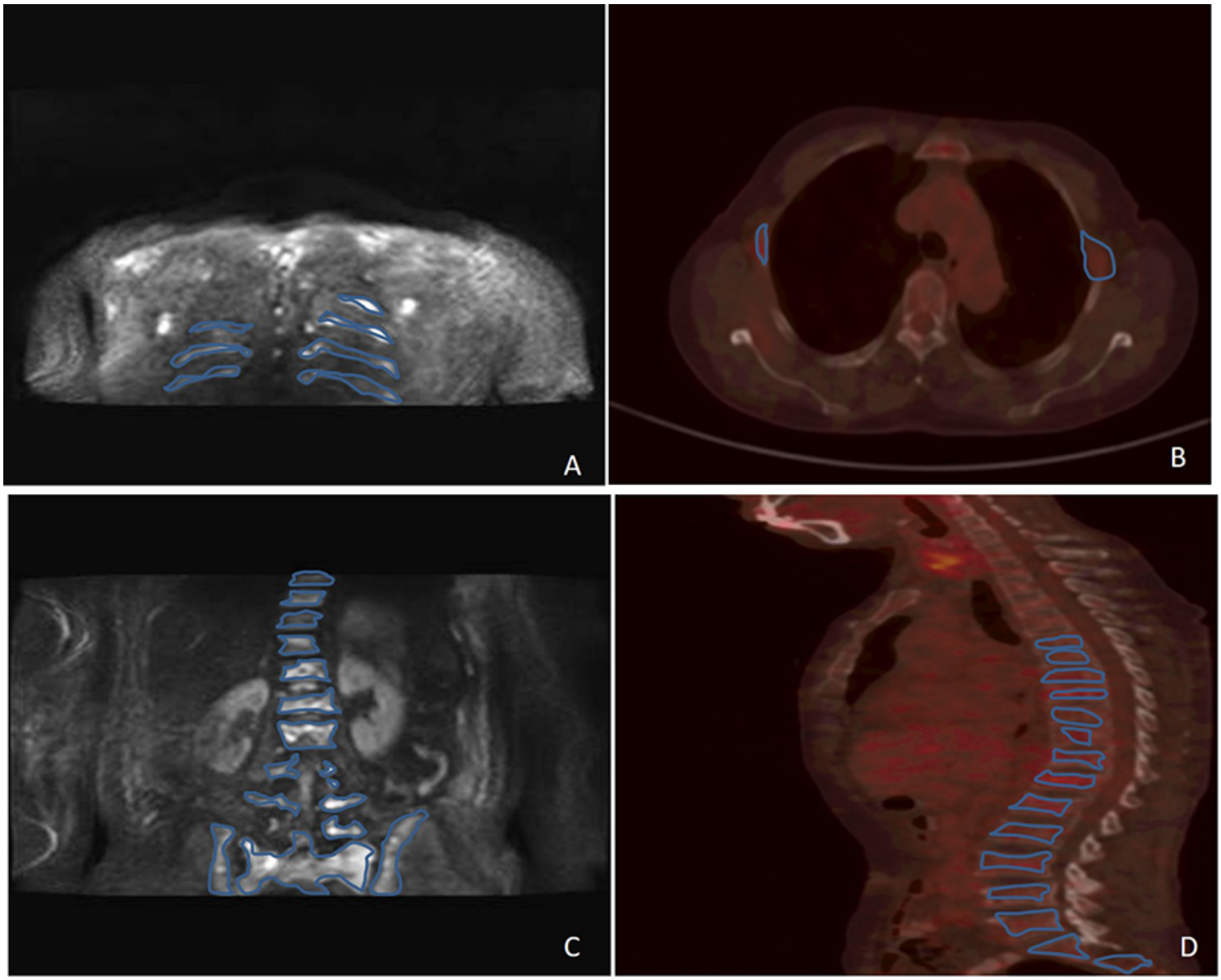

Figure 3

A 56-year-old female patient with multiple myeloma (MM) underwent both WB-DWI and FDG PET/CT. WB-DWI (Figure 3A) led to the detection of more MM lesions in the ribs than FDG PET/CT (Figure 3B). A 67-year-old male patient with MM also underwent both WB-DWI and FDG PET/CT. All MM lesions detected by FDG PET/CT (Figure 3C) were also accurately detected by WB-DWI (Figure 3D).