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Role of whole-body diffusion-weighted imaging in evaluation of multiple myeloma

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Abstract

The evaluation of bone disease in multiple myeloma (MM) is an important topic in imaging. This study retrospectively investigated whole-body diffusion-weighted imaging (WB-DWI) in the evaluation of bone marrow infiltration and treatment response in MM.

A total of 126 patients with MM who underwent WB-DWI between January 2016 and December 2020 were enrolled. All the patients received 4-course induction chemotherapy. WB-DWI was performed before and after chemotherapy to measure the apparent diffusion coefficient (ADC) values. According to gender and Revised International Staging System (RISS) staging groups, the relationship between ADC value and bone marrow plasma cell infiltration ratio before treatment were explored using Spearman and Pearson correlation coefficients. Comparison of ADC values before and after treatment according to different chemotherapy regimens and treatment response was performed by 2-independent samples non-parametric tests and *t* test.

There was a negative correlation between the ADC value and the degree of bone marrow infiltration and this was statistically significant ($r=-0.843$, $P<.001$). In different gender and RISS groups, ADC value before treatment was negatively correlated with the proportion of plasma cell infiltration (male, $r=-0.849$; female, $r=-0.836$; Stage I, $r=-0.659$; Stage II, $r=-0.870$; Stage III, $r=-0.745$; all $P<.001$). The ADC values of all subjects increased to varying degrees after 4-course induction chemotherapy, including different chemotherapy regimens and treatment responses (all $P<.05$ except for progressive disease group).

The ADC value was negatively correlated with the degree of bone marrow infiltration in different gender and RISS stages. The ADC value increased after treatment, but it was not consistent with progressive disease group. The increase of ADC value may indicate the disease burden and outcome of MM induced chemotherapy.

Abbreviations: ADC = apparent diffusion coefficient, MM = multiple myeloma, PD = progressive disease, RISS = Revised International Staging System, WB-DWI = whole-body diffusion-weighted imaging.

Keywords: bone marrow, diffusion magnetic resonance imaging, examinations and diagnoses, multiple myeloma

1. Introduction

Multiple myeloma (MM) is a clonal B-cell malignancy that is characterized by abnormal proliferation of plasma cells in the bone marrow and abnormal immunoglobulins in the blood and/or urine.[1] MM is the second most common hematological malignancy,[2] accounting for about 10% of hematological malignant tumors.[3] The symptoms of MM have been widely concerned, among which bone diseases have attracted much attention in recent years. About 90% of MM patients will show osteolytic bone disease in the progression.[4] In the last decade, the prognosis of MM patients has been greatly improved, but bone complications still seriously affect the life quality of MM patients.[5] However, accurate detection and quantitative evaluation of MM bone disease have always been an important topic for medical imaging.

Since the application of whole-body diffusion-weighted imaging (WB-DWI) in clinical work, the diagnosis of MM bone disease has been one of the development directions of WB-DWI.[6] Apparent diffusion coefficient (ADC) value is expected to map the effect of MM bone disease on bone microstructure.[7,8] ADC reflects the diffusion of water molecules,[9] so theoretically, the proliferation of tumor cells in MM bone lesions is negatively correlated with the diffusion rate of water molecules.[10] The relationship between ADC value and disease burden of MM (the proportion of bone marrow plasma cell infiltration), still needs to be further explored. Whether ADC value will increase after treatment under different conditions also needs further evidence.

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Ethics approval and consent of the patient to participate in the present study have been obtained. This study has been approved by the Institutional Review Board at our hospital (approval no. 2020-323). Written informed consent for the publication of this report and the accompanying images was also obtained from the patient.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

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Table 1

WB-DWI scanning parameters.

	DWI coronal	DWI axial	T2 STIR coronal	T2 FSE sagittal	T1 Dixon coronal	T1 FSE sagittal
Number of slices	48	36	24	12	24	12
FOV	400	400	400	400	400	400
Thickness (mm)	1.5	3	3	3	3	3
TR (ms)	5200	5200	8600	2320	480	420
TE (ms)	110	80	50	50	40	50
TI (ms)	180	160	150	160		
Image matrix	128 × 128	256 × 256	256 × 256	128 × 128	256 × 256	256 × 192
Number of excitations	4	2	2	2	2	2
b values (s/mm^2)	0/1000	0/1000				
Acquisition time (min)	4	2	2	2	1	2

FOV = field of view, FSE = fast spin echo, STIR = short time inversion recovery, TE = echo time, TI = inversion time, TR = repetition time, WB-DWI = whole-body diffusion-weighted imaging.

Further research, including artificial intelligence of neural network, needs to be based on such quantitative results.[11]

ADC value as a quantitative parameter of WB-DWI, to clarify ADC potential changes in MM bone disease will be expected to assess the severity of MM and treatment response, all of which will contribute to the management of MM. This study aimed to analyze the ADC values of patients with MM who underwent WB-DWI, so as to provide further support for ADC in the evaluation of MM bone marrow infiltration and the treatment response of induction chemotherapy.

2. Subjects and methods

2.1. Patients

A retrospective analysis of patients with MM was performed between January 2016 and December 2020 at our hospital. This study was approved by the ethics committee of our institution. Written informed consent to publish their case details and accompanying images were obtained from all patients.

Inclusion criteria: patients aged between 18 and 70 years; patients who met the diagnostic criteria of MM according to the 2014 updated criteria from the International Myeloma Work Group[12]; all the MM patients were newly diagnosed; all enrolled MM patients underwent first WB-DWI before induction chemotherapy; the second WB-DWI was performed within 1 week after 4 courses of induction chemotherapy; the interval between bone marrow puncture and WB-DWI was within 1 week.

Exclusion criteria: patients with diffuse bone diseases other than MM; WB-DWI did not comply with the standard scanning protocol; MM patients with extramedullary lesions; MM patients who have been treated before WB-DWI examination, and the treatment methods include chemotherapy, radiotherapy, stem cell transplantation, surgery, and so on.

2.2. Treatment

All patients received 4 courses of induction chemotherapy regardless of whether they would receive autologous stem cell transplantation or not. Induction chemotherapy for all patients is in one of the following 3 regimens: VD = bortezomib and dexamethasone; VCD = bortezomib, cyclophosphamide, and dexamethasone; VTD = bortezomib, thalidomide, and dexamethasone. Treatment response was assessed by the National Comprehensive Cancer Network guidelines for MM.[13]

2.3. WB-DWI examination

WB-DWIs were performed on a 3.0 T Ingenia MR imaging scanner (Philips, The Netherlands) with a rolling table platform,

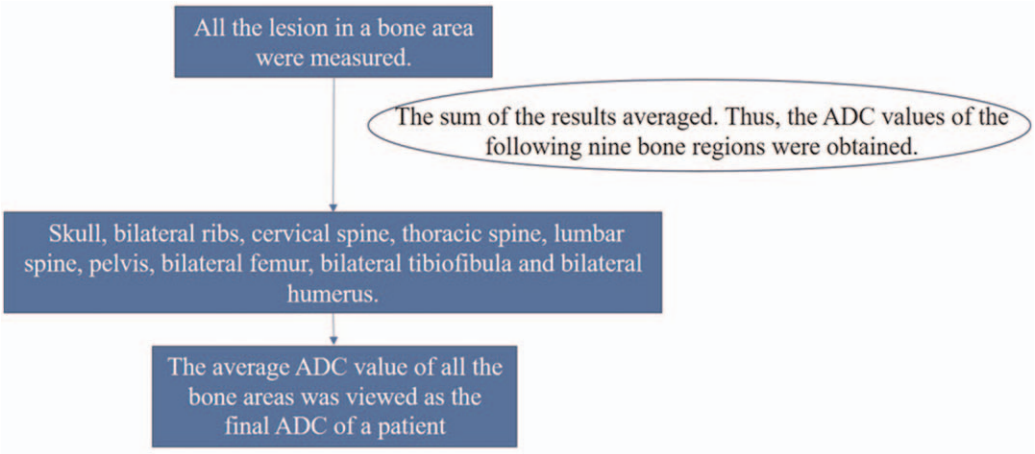

Figure 1. Flow chart of measuring ADC value. ADC = apparent diffusion coefficient.

integrated coil, 2 surface coils, head coil, and neck coil. The scanning protocol included T1WI, T2 STIR, and DWI (Table 1). Supine position, head first. The whole-body imaging was divided into 6 sections (head, chest, abdomen, pelvis, thigh, and shank). The whole spine scan was divided into 3 sections: cervical spine, thoracic spine, and lumbosacral spine. The whole scanning time was about 45 minutes.

2.4. WB-DWI data processing

The images were processed by EWS workstation (Philips, The Netherlands). The whole body was divided into 9 bone regions, including skull, bilateral ribs, cervical spine, thoracic spine, lumbar spine, pelvis, bilateral femur, bilateral tibiofibular, and bilateral humerus. If a region had 1 or more abnormal signals >5 mm, it was considered to be a lesion. If diffuse lesions are found in 1 bone, the bone will be regarded as a lesion. The average ADC value of all lesions in a bone area is the ADC value of that bone area. The average ADC value of all the bone areas was viewed as the final ADC of a patient (Fig. 1). The region of interest (ROI) was selected in the center of the lesion on the maximum level as far as possible, avoiding measurement at the edge to avoid heterogeneous signals. The average value of 3 measurements was the ADC value. Delineation of ROI and measurement of ADC values were performed by a single attending radiologist.

2.5. Histological assessment

Bone marrow biopsy was performed by a single attending hematologist. The interval between puncture and WB-DWI examination before induction chemotherapy was not more than 3 days. Bone marrow smear was evaluated by a single attending pathologist. The degree of bone marrow infiltration was assessed by the percentage of primitive or immature plasma cells in bone marrow smear.

2.6. Statistical analysis

Data were analyzed using SPSS 21.0 (SPSS Inc.). Continuous variables were expressed as mean ± standard deviation or median (interquartile range) according to whether they were normal distribution. Categorical variables were expressed as frequency (percentage). For the patient who had taken WB-DWI before and after treatment, the ADC values were compared with 2-independent samples non-parametric tests and *t* test. Spearman and Pearson correlation coefficients were used to analyze the

Table 2

Demographic and clinical characteristics.

Variable	Patients (n = 126)
Age (years)	58.67 ± 8.18
Male/female	83 (65.9%)/43 (34.1%)
RISS stage	
I	32 (25.4%)
II	40 (31.7%)
III	54 (42.9%)
Chemotherapy	
Bortezomib and dexamethasone (VD)	50 (39.7%)
Bortezomib, cyclophosphamide, and dexamethasone (VCD)	33 (26.2%)
Bortezomib, thalidomide, and dexamethasone (VTD)	43 (34.1%)
Treatment response	
Strict complete response (sCR)	18 (14.3%)
Complete response (CR)	36 (28.6%)
Very good partial response (VGPR)	29 (23.0%)
Partial response (PR)	17 (13.5%)
Minor response (MR)	7 (5.6%
Stable disease (SD)	10 (7.9%)
Progressive disease (PD)	9 (7.1%)

Data are expressed as mean ± standard deviation, median (interquartile range), or n (%).
RISS = Revised International Staging System.

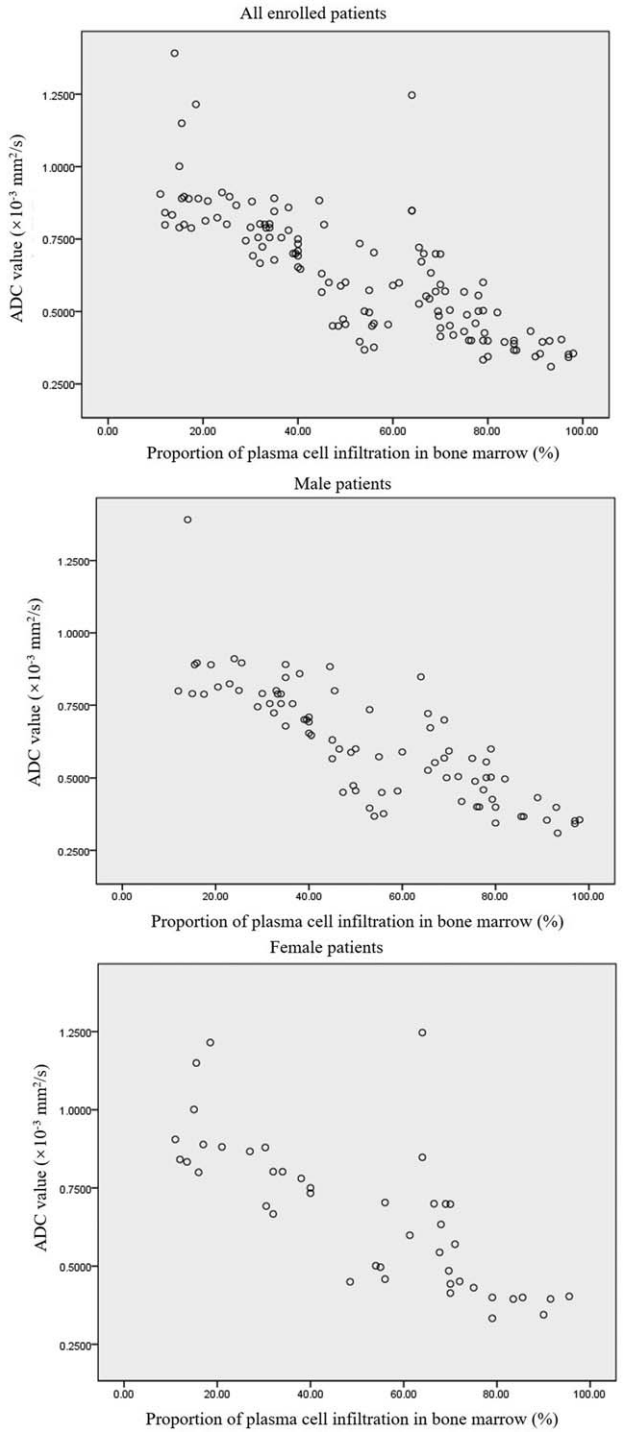

Figure 2. Scatter plot of the relationship between the proportion of plasma cell infiltration in bone marrow and ADC value of different genders. In different gender groups, scatter plot showed a significant negative correlation trend. ADC = apparent diffusion coefficient.

correlation between the ADC value and the degree of bone marrow infiltration. $P < .05$ was considered as statistically significant.

3. Results

3.1. Baseline characteristics

A total of 126 patients with MM who underwent WB-DWI were included in the study. Their mean age was 58.67 ± 8.18 years and 65.9% were male. The patients' clinical characteristics including Revised International Staging System (RISS) stage, chemotherapy regimen, and treatment response are shown in Table 2.

3.2. Correlation between ADC value and bone marrow infiltration of plasma cells

All the patients underwent bone marrow puncture at the right ilium before their treatment regimen. There was a negative correlation between the ADC value and the degree of bone marrow infiltration and this was statistically significant (r = –0.843, $P < .001$). There were negative correlations between the ADC value and the degree of bone marrow infiltration in different genders (Fig. 2 and Table 3; male, r = –0.849, $P < .001$; female, r = –0.836, $P < .001$). There were negative correlations between the ADC value and the degree of bone marrow infiltration in different RISS stages (Fig. 3 and Table 4; Stage I, r = –0.849, $P < .001$; Stage II, r = –0.870, $P < .001$; Stage III, r = –0.745, $P < .001$).

3.3. The change of ADC value before and after treatment

All the patients underwent WB-DWI examination before and after 4-course induction chemotherapy, 83 (65.87%) had strict complete response, complete response, or very good partial response. The ADC values after treatment were significantly higher than those before treatment ($P < .001$). Similar results were obtained in different treatment regimens (VD, VCD, and VTD; Fig. 4 and Table 5) and different treatment responses (strict complete response, complete response, very good partial response, partial response, minor response, stable disease, and progressive disease [PD]; Figs. 5 and 6 and Table 6) with all the *P* values were less than .05 except for PD treatment response patients.

4. Discussion

The aim of this study was to retrospectively analyze the data of patients with MM who underwent WB-DWI to provide more information to support the ADC value to evaluate bone marrow infiltration and treatment response. The results showed a clear negative correlation between the ADC value and the degree of bone marrow infiltration in all 126 newly diagnosed patients

Table 3

Correlation between ADC value and proportion of bone marrow plasma cell infiltration in MM patients of different genders.

Subjects	ADC value ($\times 10^{-3}$ mm^2/s)	Plasma cell infiltration (%)	r	*P* value
All	0.6157 (0.4504–0.7992)	54.00 (33.23–73.29)	–0.843	<.001*
Male	0.6004 (0.4539–0.7887)	51.50 (34.75–75.70)	–0.849	<.001*
Female	0.6953 (0.4503–0.8392)	56.00 (30.35–70.00)	–0.836	<.001*

ADC = apparent diffusion coefficient, MM = multiple myeloma.
* Statistically significant.

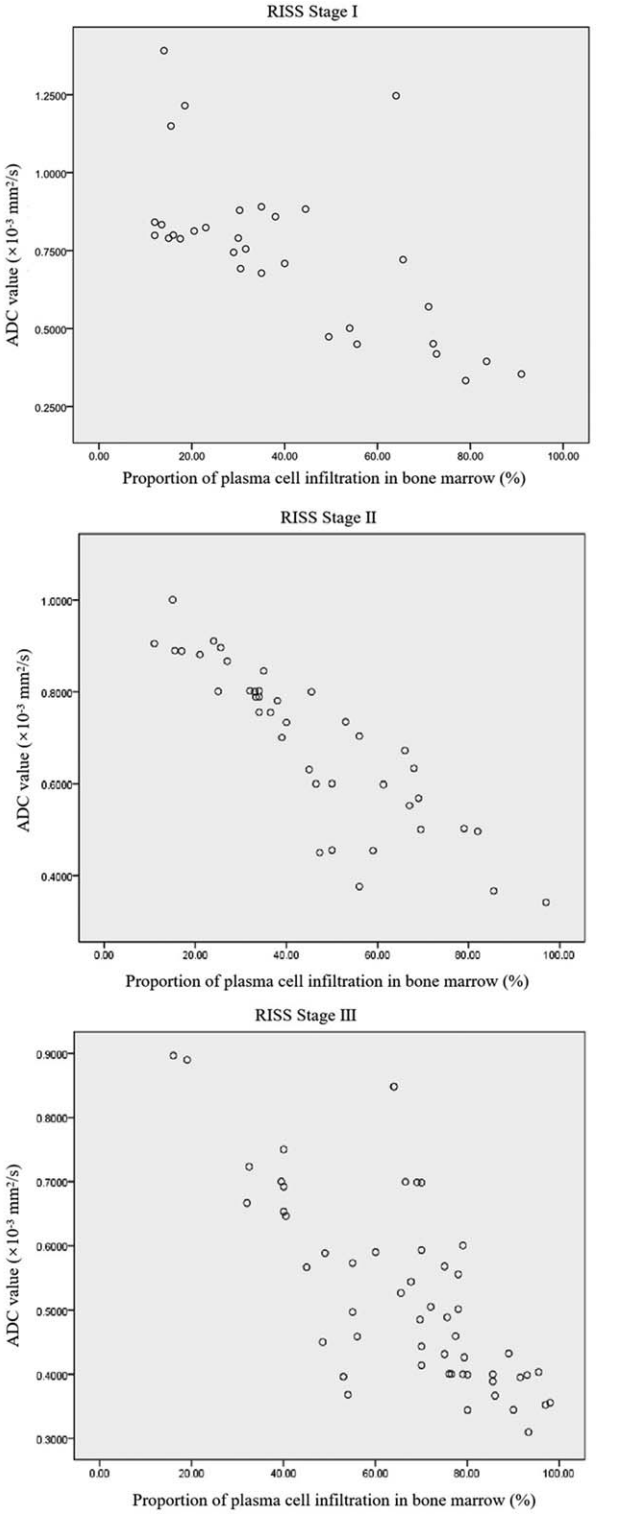

Figure 3. Scatter plot of the relationship between the proportion of plasma cell infiltration in bone marrow and ADC value of different RISS Stages. In different RISS staging groups, scatter plot showed a significant negative correlation trend. ADC = apparent diffusion coefficient, RISS = Revised International Staging System.

Table 4

Correlation between ADC value and proportion of bone marrow plasma cell infiltration in MM patients of different RISS stages.

RISS stage	ADC value ($\times 10^{-3}$ mm^2/s)	Plasma cell infiltration (%)	r	*P* value
All stages	0.6157 (0.4504–0.7992)	54.00 (33.23–73.29)	−0.843	<.001*
Stage I	0.7890 (0.5184–0.8546)	33.3 (17.75–61.90)	−0.659	<.001*
Stage II	0.6909 ± 0.1733	45.56 ± 21.02	−0.870	<.001*
Stage III	0.4927 (0.3998–0.6482)	70.00 (53.75–79.48)	−0.745	<.001*

ADC = apparent diffusion coefficient, MM = multiple myeloma, RISS = Revised International Staging System.
* Statistically significant.

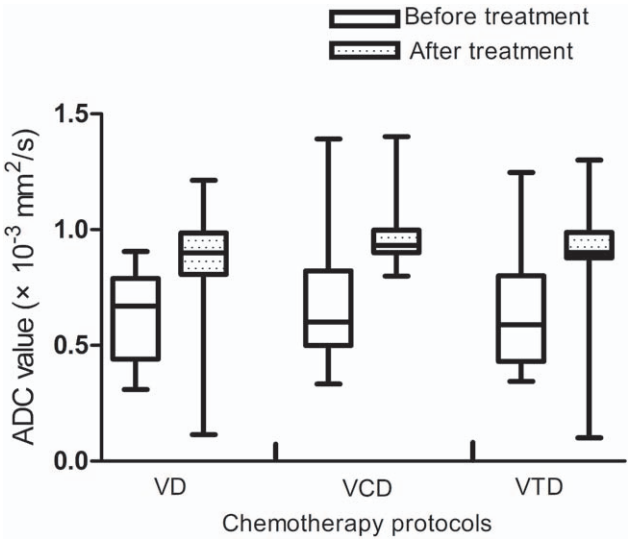

Figure 4. Box plot of ADC value before and after treatment with different chemotherapy protocols. The median ADC value of each group after treatment was significantly higher than that before treatment. ADC = apparent diffusion coefficient, VD = bortezomib and dexamethasone, VCD = bortezomib, cyclophosphamide, and dexamethasone, VTD = bortezomib, thalidomide, and dexamethasone.

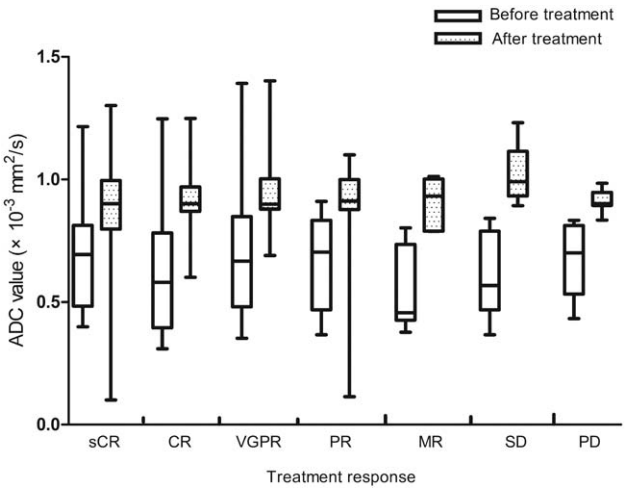

Figure 5. Box plot of ADC value before and after treatment with different treatment responses. The median ADC value of each group after treatment was significantly higher than that before treatment. ADC = apparent diffusion coefficient, CR = complete response, MR = minor response, PR = partial response, PD = progressive disease, sCR = strict complete response, SD = stable disease, VGPR = very good partial response.

before their treatment regimens. All patients underwent WB-DWI before and after induction chemotherapy, the ADC values of the MM bone lesions were shown to increase after treatment except for PD response, indicating that the change of ADC may be useful to help assess treatment responses.

The Myeloma Working Group recommends that monitoring blood and urine M protein can be used as a standard for treatment response of MM. However, there are some problems with this approach, such as in cases of non-secretory myeloma, or extramedullary myeloma lesions, which can be difficult to evaluate by serological markers.[14] The demand for curative evaluation has resorted to imaging. Studies now pay close attention to functional magnetic resonance imaging in disease diagnosis and therapeutic evaluation.[15–17]

ADC is affected by the microstructure of bone marrow, especially the primitive and immature plasma cells in MM.[18] In this study, WB-DWI may provide a useful tool for evaluating bone marrow infiltration before treatment. In different gender and RISS staging groups, ADC value of WB-DWI was significantly correlated with the proportion of bone marrow plasma cell infiltration. This result is consistent with previous studies that support the use of WB-DWI.[9,19] ADC value was taken as the average of all major lesions in the whole bone which made the ADC value more representative. The correlations in different gender and RISS groups also provided a more reliable basis for the relation of WB-DWI imaging and bone marrow microenvironment through ADC.

The preliminary results of the 126 patients in this study that underwent WB-DWI before and after treatment suggests that WB-DWI may be feasible in the evaluation of treatment effect. This result is consistent with other studies that show that DWI

Table 5

Difference of ADC value before and after different induction chemotherapy.

Chemotherapy protocols	ADC value ($\times 10^{-3}$ mm^2/s)		Z/t	*P* value
	Before treatment	After treatment		
All	0.6157 (0.4504–0.7992)	0.9018 (0.8772–0.9904)	−9.188	<.001*
VD	0.6694 (0.4404–0.7892)	0.8993 (0.8070–0.9858)	−5.671	<.001*
VCD	0.6007 (0.4990–0.8217)	0.9321 (0.9003–0.9979)	−5.012	<.001*
VTD	0.5900 (0.4311–0.8002)	0.9004 (0.8776–0.9882)	−5.289	<.001*

ADC = apparent diffusion coefficient, VCD = bortezomib, cyclophosphamide, and dexamethasone, VD = bortezomib and dexamethasone, VTD = bortezomib, thalidomide, and dexamethasone.
* Statistically significant.

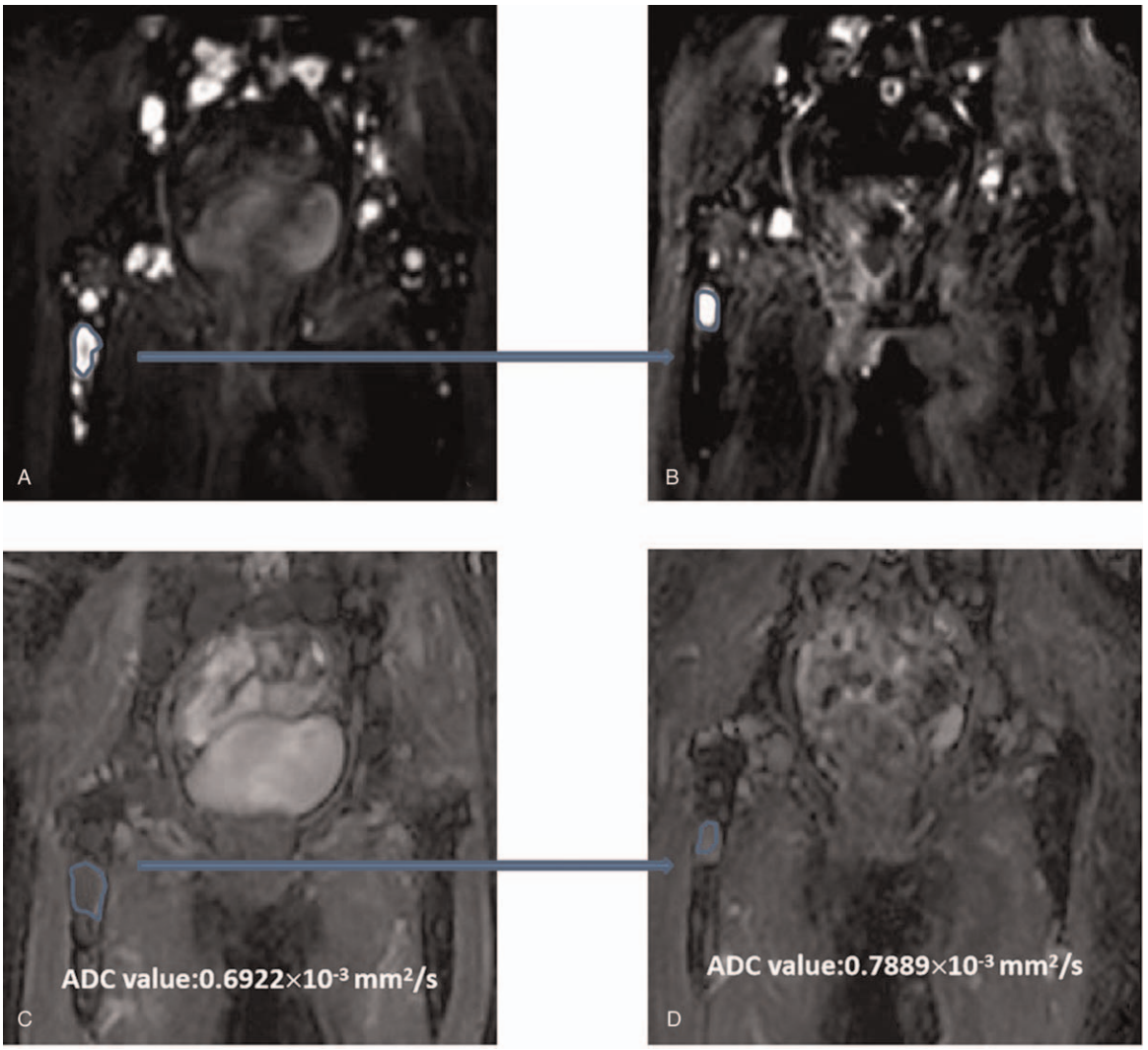

Figure 6. Change of ADC value in right upper femur lesion before and after treatment. A 56-year-old male patient, the clinical diagnosis was multiple myeloma, RISS Stage III. After 4-course induction chemotherapy, the ADC value of right femoral lesions increased from $0.6922 \times 10^{-3}\,mm^2/s$ to $0.7889\,mm^2/s$. ADC = apparent diffusion coefficient, RISS = Revised International Staging System.

Table 6

The change of ADC value in different treatment response.

	ADC value ($\times 10^{-3}$ mm²/s)			
Treatment response	**Before treatment**	**After treatment**	**Z/t**	***P* value**
All	0.6157 (0.4504–0.7992)	0.9018 (0.8772–0.9904)	−9.188	<.001*
sCR	0.6770 ± 0.2187	0.9008 (0.7979–0.9953)	−3.027	<.001*
CR	0.5801 (0.3949–0.7815)	0.9007 (0.8696–0.9689)	−5.232	<.001*
VGPR	0.6667 (0.4812–0.8481)	0.8993 (0.8789–1.0027)	−4.681	<.001*
PR	0.6660 ± 0.1903	0.9123 (0.8773–0.9993)	−2.817	<.001*
MR	0.5467 ± 0.1676	0.9115 ± 0.9220	−6.364	.001*
SD	0.5933 ± 0.1675	1.0145 ± 0.1083	−6.065	<.001*
PD	0.6615 ± 0.1459	0.7126 ± 0.4626	0.065	.950

ADC = apparent diffusion coefficient, CR = complete response, MR = minor response, PD = progressive disease, PR = partial response, sCR = strict complete response, SD = stable disease, VGPR = very good partial response.

* Statistically significant.

examination can assess the tumor treatment effect.[20,21] Quantification of imaging findings can be performed by observing changes in WB-DWI signal intensity and ADC values. To a certain extent, the trend of ADC value change can predict the prognosis of the patients. The ADC value of the tumor is in inverse proportion to the density of the cells. Furthermore, the ADC value increases continuously as the tumor burden decreases.[18]

In our study, besides the change of ADC value of all subjects before and after treatment, the changes of ADC in different treatment regimens and response groups are studied. After induction chemotherapy, the ADC of intra-medullary lesions in MM patients increased significantly except for PD, which was preliminarily confirmed. Yamada et al[22] found that ADC value of MM treatment responders differed more significantly than that of non-responders ($0.154 \pm 0.386 \times 10^{-3}$ mm^2/s vs $-0.307 \pm 0.424 \times 10^{-3}$ mm^2/s, $P = .003$). In addition, it has been proved that ADC value was negatively correlated with survival time ($r = -0.641$, $P < .001$).[23] As for the treatment response of PD, the average ADC value increased after treatment, but there was no statistical significance compared with the ADC value before treatment. In 9 cases of PD, the increase of ADC value after treatment was slight in most patients, and even increased in some cases after treatment. Similarly, the ADC value of soft tissue sarcomas with different histological grades decreased when the disease progressed.[24]

This study has some limitations. The detection efficiency of WB-DWI in intra-medullary lesions of MM should be further studied in larger multicenter based studies. The texture feature of WB-DWI combined with the change of ADC value to predict the treatment response of MM may be an issue that needs to be confirmed by large samples in the future.

5. Conclusion

This study exhibits that there were negative correlations between the ADC value and the degree of bone marrow infiltration in both genders and different RISS stages. The ADC values increased significantly after induction chemotherapy with different treatment responses except for PD response. ADC may be useful to help assess disease burden and treatment response of MM. However, we need to further explore the manifestations of ADC value in WB-DWI along the MM disease process.

Author contributions

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