Correlations Between Apparent Diffusion Coefficient Values of WB-DWI and Clinical Parameters in Multiple Myeloma

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Research article

Keywords: Apparent diffusion coefficient, Diffusion-weighted imaging, FISH, Multiple myeloma, Therapeutic response

Posted Date: October 14th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-89493/v1>

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Version of Record: A version of this preprint was published at BMC Medical Imaging on June 8th, 2021. See the published version at <https://doi.org/10.1186/s12880-021-00631-2>.

Abstract

PURPOSE: Whole-body diffusion-weighted imaging (WB-DWI) is a method for evaluating bone marrow infiltration in multiple myeloma (MM). This study seeks to elucidate the correlation between the apparent diffusion coefficient (ADC) value and some selected clinical parameters.

MATERIALS AND METHODS: 101 Chinese patients with MM who had undergone WB-DWI from May 2017 to May 2019 were enrolled in this study. The ADC values of the MM lesions and the clinical parameters were quantified at the first (baseline) visit and after four-course induction chemotherapy. Multiple linear regression and logistic analyses were carried out to find the implicit inherent relationships within the patients' data.

RESULTS: The paired Wilcoxon test showed that the ADC values at the baseline visit (ADC_0) were significantly lower than the values after four-course induction chemotherapy (ADC_{4c}) ($p < 0.001$), including different therapeutic responses. The Revised International Staging System (RISS) stage, type of MM, and $\beta 2$ -microglobulin ($\beta 2$ -MG) were predictors of clinically significant increases or decreases in the ADC values ($p < 0.05$). Multiple linear regression showed that the ADC_0 was negatively associated with $\beta 2$ -MG ($p = 0.001$) and immunoglobulin heavy chain gene rearrangement ($p = 0.012$), while the RISS Stage ($p = 0.001$), type IgG λ ($p = 0.005$), and albumin were negatively associated with ADC_{4c} ($p = 0.010$). The impacts of the therapeutic response were associated with ADC_0 and immunoglobulin heavy chain gene rearrangement ($p = 0.001$).

CONCLUSION: The ADC values of WB-DWI may be associated with clinical parameters of MM including the fluorescence in situ hybridization (FISH) result, and may be useful in the prognosis of patients with MM.

TRIAL REGISTRATION: ChiCTR2000029587

Introduction

Multiple myeloma (MM) is an abnormal proliferation of plasma cells characterized by hypercalcemia, renal insufficiency, anemia, and bone disease^[1], which can result in various complications and high mortality.^[2]

Magnetic resonance (MR) imaging is usually performed to evaluate the burden of disease in patients with MM and to make therapeutic decisions.^[3] Although conventional MR imaging analysis has been used for many years to assess the disease burden^[4], it cannot fully explain the clinical features of MM intramedullary lesions. Whole-body diffusion-weighted imaging (WB-DWI) is a clinically applicable MRI method that adopts the short tau inversion recovery (STIR) sequence to suppress background signals.^[5] However, a fundamental limitation of DWI is the lack of relationship between imaging indicators and clinical or even genetic characteristics. However, the apparent diffusion coefficient (ADC) values may be

helpful in overcoming these limitations. The ADC value may likely provide more sensitive biomarkers for detecting changes in the microstructure that occur in the bone marrow, which may be a more accurate biomarker for the prediction of disease prognosis. Although WB-DWI has been applied to MM in some tentative studies^[6, 7], its potential application in the estimation of genetic variation in MM is not yet well established.

The purpose of this study was to investigate the associations between the ADC values of the bone marrow lesions in patients with MM and fluorescence in situ hybridization (FISH) results along with other clinical parameters. Our hypothesis was that ADC values have a degree of correlation with genetic variations (FISH results) as well as clinical and laboratory parameters and that this is related to the therapeutic response of MM.

Materials And Methods

Participants

The study was approved by the Institutional Ethics Committee of the First Hospital of Jilin University, Changchun, China. Written informed consent was obtained from the patients by email or letter. We retrospectively reviewed the Picture Archiving and Communication System for MM patients who had undergone WB-DWI during a 24-month period (May 2017 to November 2019). The inclusion criteria were as follows: 1) patients aged between 18 and 70 years; 2) patients with a diagnosis of MM according to established diagnostic criteria; 3) patients who had undergone WB-DWI performed according to our standard MM protocol; 4) patients who had received autologous stem cell transplantation; and 5) patients who had received WB-DWI before and after four courses of induction chemotherapy.

We excluded patients with bone diseases other than MM. We also excluded all imaging data with poor quality due to body movements or other artifacts.

Treatment

All patients received stem cell transplantation after induction chemotherapy. Each patient received chemotherapy as one of the following three options (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 by the National Comprehensive Cancer Network guidelines for MM, including complete response (CR), strict complete response (sCR), very good partial response (VGPR), partial response (PR), stable disease (SD) and progressive disease (PD).^[8]

MR Imaging

WB-DWIs were performed on a 3.0T Ingenia MR imaging scanner (Philips, The Netherlands) with a rolling table platform, integrated coil, two surface coils, head coil and neck coil. Multiple-station scanning is

used in the protocol. Seven scans were conducted from “head to toe”. The study protocol included fat suppressed T2-weighted short time inversion recovery (STIR) acquired separately in the coronal plane for the head-neck, chest, abdomen, pelvis, femur, tibia and feet districts, successively merged to create a single “whole body” image. STIR were conducted with the following parameters: repetition time (TR)/echo time (TE)/inversion time (TI), 8600/60/170 ms; image matrix, 290×310; field of view (FOV), 400mm; number of excitations (NEX), 4; slice thickness/gap, 7/0mm; number of slices, 24; and acquisition time, 3 mins. Echo-planar DWI were conducted with the following parameters: b value, 0 and 1000 s/mm²; repetition time (TR)/echo time (TE)/inversion time (TI), 5200/106/180 ms; image matrix, 128×128; field of view (FOV), 400mm; number of excitations (NEX), 4; slice thickness/gap, 7/0mm; number of slices, 24; and acquisition time, 4 mins. The images obtained with a value of b = 1000 s/mm² were then reformatted into maximum intensity projection (MIP) and evaluated by inversion of the grayscale. The total scan time was close to 45 mins.

Data Processing

The patient will be excluded from the study once the unexplained high signal outside the skeleton is found on DWI images. The ADC values were measured in six areas (skull, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, bilateral ilium, ribs). Using region of interest (ROI) analysis, we measured the ADC₀ and ADC_{4c} of the entire cross-sectional area of all the lesions. The software automatically outlines the lesions, including all the layers showing the lesions (Figure 1). When the automatic sketch is not accurate, manual modification of the accurate contour of the lesion is required. When the lesion is diffuse, all the levels of the whole bone need to be outlined. The average ADC value of all lesions in each region is the ADC value in that region. If there is no MM lesion in an area, then that area will not be measured, and it will not be included in the calculation of the final ADC value. We generated six values in each subject. Altogether, out of 606 sections after exclusion (based on actual lesion distribution area), only 517 sections were left for 101 patients. All measured layers included lesions. DWI data were processed and the ADC maps were generated using an EWS workstation (Philips, The Netherlands). The delineation of ROI before and after treatment ensures the consistency of measurement location to the greatest extent. The anatomical position of the lesions before and after treatment was precisely located by using T2-STIR and DWI sequence, and then the ROI of the lesions was sketched by software in the ADC map. The ROI measured by the ADC value of each lesion includes all slices of the lesion. The ROI Delineation and the ADC value was obtained by three attending radiologists, following which the average of the three ADC values was taken to exclude the variability among observers.

The results were analyzed by SPSS software (Version 14.0, IBM, Armonk, New York). The ADC₀ and ADC_{4c} including different therapeutic responses were examined with the paired Wilcoxon test. The level of plasma cell infiltration, albumin, LDH, and β2-MG were examined with the paired t-test. Multiple linear regression and logistic analysis were used to determine the relationships between the ADC values and the clinical variables (age, plasma cell infiltration, RISS Stage and type, albumin, LDH, and serum β2-MG)..

The impacts of the therapeutic response were investigated using multiple logistic regression. P-values of <0.05 were considered statistically significant.

Results

Demographic and Clinical Characteristics

A total of 101 patients with MM were included in the study. Table 1 shows their demographic and clinical characteristics including the RISS staging and type of the entire cohort at the baseline visit. MM in this study affected men more often than women. Table 2, Figures 1, 2, and 3 show the analysis of variance of the mean ADC values in patients including different therapeutic responses before and after chemotherapy. The ADC_0 was significantly lower than the ADC_{4c} ($P < 0.001$). Plasma cell infiltration at baseline was significantly higher after chemotherapy (Table 2 and Figure 4).

Imaging Data

Logistic regression demonstrated the influence of clinical parameters on increases and decreases in ADC values after chemotherapy, including age ($p = 0.289$), gender ($p = 0.634$), RISS Stage ($p = 0.001$), type ($p = 0.005$), albumin ($p = 0.619$), LDH ($p = 0.646$), $\beta 2$ -MG ($p = 0.002$), p53 deletion ($p = 0.912$), IGH rearrangement ($p = 0.007$), q21 amplification ($p = 0.997$), RB1 deletion ($p = 0.280$), and p32 deletion ($p = 0.634$) (Table 3). Multiple linear regression showed that $\beta 2$ -MG ($\beta = -0.038$) and IGH rearrangement ($\beta = -0.107$) were correlated with ADC_0 (Table 4). RISS Stage ($\beta = -0.107$), IgG λ ($\beta = -0.151$) and albumin ($\beta = -0.009$) were correlated with ADC_{4c} (Table 5).

Multiple logistic regression showed that the main predictors of treatment effect in this study included ADC_0 and (IGH) gene rearrangement (Table 6). ORs (and 95% CIs) of treatment response with stratification of ADC_0 and IGH gene rearrangement. The reference group was Group sCR since their treatment response was better than that in other groups. Compared to ADC values of $0.9 \times 10^{-3} \text{ mm}^2/\text{s}$ and above, ADC values of less than $0.8 \times 10^{-3} \text{ mm}^2/\text{s}$ were less likely to produce a VGPR treatment response. Compared to ADC $0.7 \times 10^{-3} \text{ mm}^2/\text{s}$ and above, ADC values between $0.3 \times 10^{-3} \text{ mm}^2/\text{s}$ and $0.4 \times 10^{-3} \text{ mm}^2/\text{s}$ (OR 1.268, 95% CI: 0.445-1.116) were more likely to produce a PD treatment response. Patients with p53 (OR 1.828, 95% CI: 1.905-3.445) and RB1 (OR 1.492, 95% CI: 0.067-1.992) deletions were more likely to have a PD treatment response than other genetic variations.

Discussion

This is a retrospective study that explored the hypothesis of whether or not clinical variables and FISH-derived metrics are associated with the ADC value of WB-DWI in patients with MM. Our results indicate a correlation between the ADC value and genetic variation and suggest that both are related to the clinical outcome of MM patients. In contrast to previous studies, this study investigates not only the clinical indicators that affect the ADC value of WB-DWI but also the relationship between ADC value and MM

treatment response. It is worth mentioning that it also includes the derivative results of FISH detection, which are not addressed in previous studies. However, due to its retrospective nature, the results of the current study need to be validated by future research. If our results are confirmed, FISH-derived metrics and ADC may have significant roles in improving the comprehensiveness of prognosis as well as in guiding therapeutic options in MM.

Whole-body CT, PET / CT, and other examination methods are applied to MM bone diseases, and they have good detection capabilities in cortex, medulla, and extramedullary diseases.^[9] Compared with these methods, WB-DWI has its merits and limitations. WB-DWI, with its advantages of large imaging range and no radiation, especially the ADC value which can be used to quantify the diffusion of water molecules in tissues, has become an alternative method for the detection of bone disease in MM patients.^[5, 10] Limitations of WB-DWI include possible difficulties in focus segmentation in patients with multiple bone marrow diseases.^[5] WB-DWI is also not satisfactory for distal extremity and extramedullary lesions. However, WB-DWI has been shown to produce good consistency in the detection of bone marrow and extraosseous metastasis ($\kappa = 0.887$, agreement = 94.44%, $p = 0.001$).^[11]

Although the role of ASCT in improving the overall survival in older patients (age ≥ 65 years) is still uncertain^[12], older patients were included in the study to ensure an adequate age span. The ADC value of intramedullary lesions is affected by many factors.^[13] The quantified ADC variations of the brain and pancreas provide standard reference points for radiologists.^[14] It is inferred that age also plays an important role in the ADC value of MM. However, we found no correlation between the ADC value and patient's age.

MM progression produces a decrease in albumin and an increase in LDH and $\beta 2$ -MG.^[15] The albumin level is mainly determined by the stage of MM disease or tumor load and has prognostic significance.^[16] Therefore, the hypothesis and inference that the serum albumin, LDH, and $\beta 2$ -MG levels of MM patients are related to WB-DWI imaging features are worth pondering and verifying. Previous studies have shown that some regulatory and prognostic biomarkers such as miR-146b were negatively correlated with the albumin level^[17]. In our study, albumin was only negatively related to the ADC value after chemotherapy as the ADC_{4c} . Serum LDH is widely distributed in the body and increases with tumor proliferation. In addition, experts believe that relapse of MM may be considered aggressive if there is the presentation of several features including elevated LDH.^[18] As a result, it is reasonable to believe that LDH level is related to the activity of myeloma cells. Contrary to the results of this study, no significant correlation has been found between serum LDH level and changes in the ADC value, and also no significant linear correlation with ADC_0 and ADC_{4c} . In terms of $\beta 2$ -MG, not only is aberrant plasma cell proliferation responsible for the secretion and synthesis of $\beta 2$ -MG, but cell necrosis also releases large amounts of $\beta 2$ -MG. Wu et al^[19] have reported that the $\beta 2$ -MG levels in stage I MM were higher than those in the control group ($P < 0.05$), but lower than those in stages II and III ($P < 0.05$). However, some studies have reported that serum $\beta 2$ -MG levels alone may not indicate the full extent of the MM tumor burden before chemotherapy^[20]. Overall, with the increase in tumor load, the levels of albumin, LDH, and $\beta 2$ -MG deteriorated, resulting in an

increase of tumor cells per unit volume, the decrease of cell gap, and the limited diffusion of water molecules, which ultimately led to the decrease of the ADC value. These observations suggest that serum markers of tumor load in a subset of patients with substantial myeloma infiltration in the bone marrow should be combined with imaging information.

ISS and RISS stages reflect the disease burden of MM.^[21, 22] Moreover, the RISS staging system can predict the prognosis of patients with MM.^[23] Beksac et al^[24] found that patients with ISS stage I had a significantly better prognosis than stage II and III patients. Soekojo et al^[25] reported that when compared with the RISS, there was a high level of concordance in high-risk patients identified using FISH analysis with an independent cohort of 375 patients. It can be deduced that the RISS staging as well as the FISH results are good indicators of patient prognosis. FISH plays an important role in the prognosis and risk stratification of MM patients.^[26] Therefore, FISH test results may be as closely related to the burden of MM disease as the RISS staging^[27]. If this is true, then FISH test results may relate to the ADC values of the lesion. ADC values have been found to be correlated with tumor growth and differentiation. In a study of retinoblastoma involving 72 children, the ADC value was positively correlated with the degree of tumor differentiation ($r = 0.87$, $p = 0.007$), and negatively correlated with tumor size ($r = 0.68$, $p = 0.015$).^[28] A study of nasopharyngeal carcinoma reported similar findings: the ADC value was found to be negatively correlated with the volume of the nasopharyngeal carcinoma ($r = -0.799$, $p = 0.03$).^[29] In addition, it has been found that the ADC value is also related to the metabolism of the tumor. The level of CH / Cr in cervical squamous cell carcinoma is negatively related to the ADC value ($r = -0.662$, $p = 0.001$).^[30]

The correlation between FISH-derived measures and ADC values in MM have not been previously evaluated. However, correlations between ADC values and genetic variations are found in other diseases. He et al^[31] found the mean ADC value of HER2-positive gastric cancers was significantly higher than those of HER2-negative tumors (1.211 vs. 0.984 mm²/s, $P = 0.020$). Therefore, we have hypothesized that there is a correlation between some genes and the ADC values in MM. However, this result is limited to single-locus gene changes. Studies have shown that IGH rearrangement can affect related genes and trigger the autocrine mechanism of tumors^[32], leading to disease progression^[33]. This may be the cause of the increased tumor load that leads to a decrease in the ADC value. Cui et al^[34] found that specific sets of miRNAs can be considered as biomarkers for distinguishing MM with 1q21 amplification. Patients with 1q21 amplification were more likely to have abnormal amplification of RB1 and p53 than those without this condition. Chatonnet et al^[35] found that specific genes on 1q21 are involved in the transcription factor network that controls cell proliferation, which leads to excessive proliferation of cancer cells, thereby affecting the ADC value of bone marrow lesions. But in our study, only IGH rearrangement was correlated with ADC₀. It has been suggested that IGH-MMSETMB4-2/MB4-3 transcripts of fusion genes in t(4;14) multiple myeloma indicate a poor prognosis^[36], but other studies found that IGH deletion has no influence on the prognosis of MM. Regarding the negative correlation between ADC₀ and IGH rearrangement observed in this study, the decrease in ADC value often indicates

that the disease burden is heavier. However, whether or not the IGH rearrangement is related to disease progression needs to be investigated in a different study with larger samples.

Whether ADC values before treatment or at the baseline visit (ADC_0) can predict the outcome of patients is an intriguing question. MR-based texture analysis may be helpful for the evaluation of MM patients' response to treatment.^[37] In addition, this study has shown that the average ADC of patients in the CR / VGPR group increased significantly after induction chemotherapy.^[38] However, Park et al^[39] consider that MR imaging is useful in the evaluation of PD (sensitivity 94.7%, specificity 84.2%), but the evaluation of CR is not satisfactory (sensitivity 4.5%, specificity 98.1%), which also involves the information of the ADC map. When the baseline ADC value was $0.808 \times 10^{-3} \text{ mm}^2 / \text{s}$, ADC had the specificity of 68.05% and sensitivity of 54.09% in predicting the increase in ADC after treatment.^[40] Determination of ADC before initiating treatment may predict the outcome of treatment to some extent.

Conclusion

This study showed significant correlations between the ADC value and FISH results as well as other clinical parameters including the treatment response. However, additional research is needed to further define the inter-relationships among the ADC value, FISH results and the other clinical indicators.

Abbreviations

MM = Multiple myeloma; ADC = Apparent Diffusion Coefficient; WB-DWI = Whole-Body Diffusion-Weighted Imaging; FISH = Fluorescence in situ hybridization; LDH = Lactic dehydrogenase; $\beta 2$ -MG = $\beta 2$ -microglobulin; ADC_0 = ADC value at baseline visit; ADC_{4c} = ADC value at 4-course induction chemotherapy follow-up; ASCT = Autologous stem cell transplant; RISS = Revised international staging system; ISS = International staging system; ROI = Region of interest; CR = Complete response

sCR = Strict complete response

PR = Partial response

VGPR = Vary good partial response

SD = Stable disease

PD = Progressive disease

Declarations

Acknowledgements

Not applicable.

Author's contributions

Bei Zhang did data analysis and drafted the manuscript. Bingyang Bian designed the MR-sequences and helped write the manuscript. Zhiwei Zhao contributed to the study design and revised MR scan protocol. Zining Zhu and Fang Lin supervised the experimental process. Mingwu Lou was responsible for designing the research plan. All of the authors have read the manuscript and have approved the final version.

Funding

Not applicable.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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	101
Sex (M/F)	63/38 62.4%/37.6%
Age (mean) (yr)	57.06 ± 9.72
RISS Stage	
Stage I	11 (10.9%)
Stage II	52 (51.5%)
Stage III	38 (37.6%)
Type	
IgA λ	11 (10.9%)
IgD λ	8 (7.9%)
IgG λ	31 (30.7%)
λ	19 (18.8%)
IgA κ	11 (10.9%)
IgG κ	15 (14.9%)
κ	6 (5.9%)
Therapeutic response	
CR	35 (34.7%)
sCR	22 (21.8%)
PR	20 (19.8%)
VGPR	15 (14.9%)
SD	6 (5.9%)
PD	3 (3%)

Table 2 Within-subjects ADC value change after chemotherapy

Parameters	Baseline visit	After 4-course chemotherapy	p value
ADC value ($\times 10^{-3}$ mm ² /s)	0.8556 (0.7130-1.361)	1.0076 (0.8817-1.3336)	$\leq 0.001^*$
Therapeutic response			
CR	0.8561 (0.7890-1.3884)	1.1330 (0.9887-1.3883)	$\leq 0.001^*$
sCR	0.6772 (0.5985-0.9066)	0.9756 $\pm$ 0.2724	$\leq 0.001^*$
PR	0.8673 (0.7912-1.3301)	1.0961 $\pm$ 0.2724	$\leq 0.001^*$
VGPR	0.9555 $\pm$ 0.3326	1.0667 $\pm$ 0.2537	0.004*
SD	1.3883 (0.8290-1.3891)	1.2588 $\pm$ 0.2467	0.151
PD	0.8504 $\pm$ 0.0602	1.0206 $\pm$ 0.8934	0.089
Plasma cell infiltration (%)	44.35 $\pm$ 23.11	5.01 $\pm$ 7.62	$\leq 0.001^*$
Albumin (g/L)	34.36 $\pm$ 7.31	37.44 $\pm$ 7.03	$\leq 0.001^*$
LDH (U/L)	222.41 $\pm$ 85.29	227.94 $\pm$ 48.14	0.570
$\beta 2$ microglobulin (μ g/mL)	8.75 $\pm$ 7.15	4.27 $\pm$ 3.00	$\leq 0.001^*$

* Significant difference

Table 3 Logistic regression results evaluating the predictors of clinically meaningful ADC value increase and decrease after chemotherapy

Parameters	ADC values increase (n = 91) ^ε	ADC values decrease (n = 10) ^ε	p value
Age	1.103 (0.920 to 1.322)	0.907 (0.756 to 1.087)	0.289
Gender	1.787 (0.164 to 19.475)	0.560 (0.051 to 6.089)	0.634
RIS Stage	0.153 (0.008 to 3.074)	2.536 (1.132 to 5.684)	0.001*
Type of MM	0.394 (0.176 to 0.884)	6.542 (0.325 to 131.52)	0.005*
β2-MG	2.406 (1.094 to 5.294)	0.416 (0.189 to 0.914)	0.002*
Albumin	0.955 (0.795 to 1.146)	1.048 (0.872 to 1.258)	0.619
LDH	1.007 (0.977 to 1.038)	0.993 (0.964 to 1.023)	0.646
p53 deletion	1.257 (0.022 to 71.310)	0.796 (0.014 to 45.143)	0.912
IGH rearrangement	1.036 (0.978 to 2.012)	1.074 (1.005 to 1.995)	0.007*
q21 amplification	0 (0 to +∞)	0 (0 to +∞)	0.997
RB1 deletion	8.963 (0.167 to 48.145)	0.112 (0.002 to 5.980)	0.280
p32 deletion	62.549 (0.120 to 32.659)	0.560 (0.051 to 6.098)	0.634

^εThe values are given as the odds ratio, with 95% confidence interval in parentheses

*Significant difference

Table 4 Multiple linear regression results evaluating the effects of clinically meaningful parameters on ADC₀

Independent variables	β	SE	β	t	p value
Constant	1.298	0.036		35.788	0.001
β2 microglobulin	-0.038	0.003	-0.752	-11.782	0.001
IGH rearrangement	-0.107	0.042	-0.163	-2.546	0.012

Note: R² = 0.601, Adjusted R² = 0.593, F = 6.481, p = 0.012.

Table 5 Multiple linear regression results evaluating the effects of clinically meaningful parameters on the ADC_{4c}

Independent variables	β	SE	$\beta\%$	t	p value
Constant	1.536	0.140		10.989	≤ 0.001
RIS Stage	-0.166	0.050	-0.319	-3.350	0.001
IgG λ	-0.151	0.053	-0.277	-2.883	0.005
Albumin	-0.009	0.003	-0.251	-2.629	0.010

Note: $R^2 = 0.167$, Adjusted $R^2 = 0.141$ F = 6.910, p = 0.010.

Table 6. Factors that may affect induced chemotherapy response of MM from multivariable logistic regression.

Characteristics	Treatment response					
	CR	sCR	PR	VGPR	SD	PD
	Odds Ratio (95% Confidence Interval)					
ADC value (×10 ⁻³ mm ² /s)						
0.3≤ADC≤0.4	1.666 (3.439- 8.069)		2.047 (1.063- 1.593)	0.496 (0.631- 2.789) *	0.136 (0.280- 1.068) *	1.268 (0.445- 1.116) *
0.4≤ADC≤0.5	1.917 (3.912- 9.396)		0.110 (0.016- 0.740) *	0.755 (0.755- 1.227) *	1.811 (1.961- 6.727)	0.496 (0.208- 2.398)
0.5≤ADC≤0.6	3.817 (9.868- 14.778)		0.692 (0.115- 4.160) *	0.349 (0.129- 0.974) *	4.432 (0.427- 1.163)	1.219 (.0598- 1.530)
0.7≤ADC≤0.8	5.752 (2.178- 15.198)		1.658 (0.376- 7.304) *	0.798 (0.476- 1.232) *	7.816 (0.920- 1.335)	0.553 (0.181- 0.910) *
0.8≤ADC≤0.9	1.121 (4.730- 2.658) *		5.999 (1.761- 20.428)	0.898 (1.497- 10.687)	1.632 (3.132- 8.499)	0.990 (0.202- 1.392) *
0.9≤ADC≤1.0	0.651 (0.914- 1.716) *		1.231 (0.339- 4.466)	1.452 (3.523- 5.986) *	0.608 (0.147- 1.705) *	0.802 (0.779- 1.252) *
1.0≤ADC≤1.1	3.906 (0.879- 1.860)		3.171 (0.339- 4.466)	1.501 (2.009- 3.452) *	3.917 (3.890- 7.998)	1.054 (0.371- 1.529) *
1.1≤ADC≤1.2	2.925 (1.334- 6.776)		2.496 (7.886- 9.009)	1.453 (1.650- 2.221) *	1.595 (3.435- 4.667)	0.510 (3.445- 8.956) *
1.2≤ADC≤1.3	1.334 (6.004- 9.657) *	Reference	0.399 (0.111- 1.433)	1.562 (1.312- 9.673) *	0.110 (0.005- 1.127) *	0.849 (0.445- 1.956) *
1.3≤ADC≤1.4	1.679 (0.679- 1.679)		1.957 (0.598- 6.410)	1.024 (0.034- 1.024)	4.008 (0.008- 0.995)	1.389 (0.672- 1.334)
1.4≤ADC≤1.5	1.355 (0.066- 1.445)		1.769 (0.998- 1.884)	1.886 (0.554- 0.981)	0.776 (0.549- 1.886) *	0.679 (0.630- 1.086)
Gene variation						
p32 deletion	0.182		0.678	3.725	1.733	0.645

	(2.397-35.169)	(2.586-4.089) *	(2.245-4.682)	(1.198-4.990)	(0.009-1.879) *
P53 deletion	0.053 (1.609-10.206) *	0.942 (2.847-16.927)	3.725 (0.242-1.535)	0.359 (0.867-1.007) *	1.828 (1.905-3.445) *
RB1 deletion	1.600 (0.856-2.991)	2.104 (1.072-4.129)	1.600 (0.768-3.331)	0.290 (0.065-2.005)	1.492 (0.067-1.992) *
q21 amplification	0.050 (1.089-3.860) *	1.319 (0.639-2.723) **	4.239 (2.047-8.779) *	1.632 (0.494-5.392)	0.985 (0.181-5.355) *
IGH rearrangement	0.640 (0.278-1.475)	0.824 (0.332-2.045)	0.205 (0.074-0.565)	0.993 (0.072-2.067) *	0.346 (0.064-1.729) *

p value for the model is less than 0.001. A single asterisk (*) implies statistically significant.

Figures

Figure 1

Figure 1 A and C show MM lesions at baseline visit. Figure 1 B and D show MM lesions after 4-course chemotherapy. Figure A and B show the contour of the same MM lesion of the same patient before and after treatment, and the ADC value of the lesion increased from $(0.698 \times 10^{-3} \text{ mm}^2/\text{s})$ to $(0.796 \times 10^{-3} \text{ mm}^2/\text{s})$. Figure C and D show the extent change of MM lesions before and after treatment in the same patient, and the ADC value increased from $(0.798 \times 10^{-3} \text{ mm}^2/\text{s})$ to $(0.833 \times 10^{-3} \text{ mm}^2/\text{s})$.

Figure 2

Box plot showed ADC value before and after treatment.

Figure 3

Box plot showed ADC value of before and after treatment different therapeutic responses.

Figure 4

Box plot showed Infiltration degree of bone marrow before and after treatment.