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ORIGINAL RESEARCH

Muscle Fat Infiltration in Patients with Multiple Myeloma: A Case–Control Study

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Background: Sarcopenia in patients with hematologic malignancies has gained attention. However, muscle fat infiltration in patients with multiple myeloma (MM) has not been well studied. In this study, we showed the prevalence of computed tomography (CT)-based muscle fat infiltration in newly diagnosed MM patients.

Methods: A total of 966 participants, 138 MM patients and 828 controls, who underwent CT examinations were involved in this study. Clinical parameters, such as participants' age, sex, weight, height and laboratory test results, such as serum lipids, liver and renal function, were collected. The CT radiation attenuation of the bilateral erector spinae (ESRA) muscles and cross-sectional axial skeletal muscle (SMRA) at the medium level of the T11 vertebra were measured on axial CT images. Logistic regression analyses were performed to assess the association between MM and the risk of low muscle CT attenuation. Receiver operating characteristic curve was used to show the performance of muscle CT attenuation in identifying MM.

Results: Muscle CT attenuation in the MM group was significantly lower than in controls ($p < 0.001$). The prevalence of low muscle CT attenuation in MM patients was significantly higher than those in controls (66.7% vs 19.6%; 60.1% vs 20.4%, $p < 0.001$). MM was significantly associated with the risk of low ESRA (<36 HU) (odds ratio (OR) = 15.11, 95% confidence interval (CI): 7.76–29.39) and SMRA (<34 HU) (OR = 12.00, 95% CI: 5.91–24.39) in the fully adjusted models. Subgroup analyses in men and women both showed similar results with the overall population. The area under the curve was 0.827 for ESRA and 0.790 for SMRA in identifying MM patients.

Conclusion: Muscle fat infiltration is common in patients with MM. MM is significantly associated with the risk of muscle fat infiltration.

Keywords: multiple myeloma, muscle fat infiltration, muscle CT attenuation

Introduction

Sarcopenia, the loss of muscle mass and strength, is a significant yet often underrecognized complication in cancer patients.[1,2] Studies indicate that sarcopenia in patients with hematologic malignancies is associated with poorer lung function,[3] more chemotherapy side effects,[4] longer hospitalization,[5] poor nutrition and inflammation,[6] and shorter overall survival.[7,8] Early detection through body composition analysis (eg, computed tomography (CT)-based muscle assessment) and targeted interventions-including nutritional support and resistance exercise may mitigate muscle loss and improve clinical outcomes.[9] Given the high prevalence and adverse impact of sarcopenia in hematologic cancers, integrating muscle health monitoring into standard oncologic care is essential for optimizing patient prognosis and quality of life.

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by clonal proliferation of plasma cells in the bone marrow, leading to osteolytic bone lesions, anemia, renal dysfunction, and immunodeficiency.[10] It accounts for

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approximately 10% of all hematologic malignancies[11] and remains incurable despite advances in therapy.[12] The prevalence of sarcopenia in MM patients has been reported. Williams et al showed that sarcopenia, which was defined as ≤80% high-density muscle within the L3 psoas muscle was found in 51% MM patients who underwent autologous hematopoietic cell transplantation.[13] Some studies also showed the association between sarcopenia defined by muscle area/height square and survival, treatment toxicity, and functional outcomes in MM patients.[7,14–17]

Most of previous studies reported the prevalence of sarcopenia defined by muscle area (32.5%-86.8%),[13–17] and focused on the association between muscle mass (eg, muscle area) and outcomes in MM patients. Muscle fat infiltration has increasingly become a subject of scientific interest in recent years. Interestingly, two recent studies showed that muscle radiodensity, rather than muscle area or muscle mass, was associated with overall survival in MM patients.[18,19] However, to our knowledge, only one study in Germany reported the prevalence of low muscle density or muscle fat infiltration in MM patients (51%).[19] Its prevalence in Asian countries is unknown. In addition, MM patients are often older, which is also a critical factor of sarcopenia or muscle fat infiltration. It is also unclear whether MM patients had a higher risk of muscle fat infiltration than control subjects. Muscle radiodensity remains under investigation in patients with hematologic malignancies. Therefore, in this case–control study, we reported the prevalence of computed tomography-based muscle fat infiltration in MM patients and investigated whether MM was related to higher risk of muscle fat infiltration compared to controls.

Materials and Methods

Study Population

Participants with pathologically confirmed newly diagnosed MMs who were treated at our institution between 2019 and 2021 and underwent computed tomography (CT) were included. MM was diagnosed according to the criteria of the International Myeloma Working Group (IMWG). Age- and sex-matched controls (1:6) were randomly selected from non-multiple myeloma adults (n = 1386) who underwent thoracic/abdominal CT scans including the T11 vertebra using Propensity Score Matching (exact matching with a tolerance level of 0.02 and without replacement). Patients with other type of cancer, cachexia or other hematologic diseases were excluded. The flowchart for the inclusion of participants is shown in Figure 1. Ethics approval was obtained from the Affiliated Hospital of Nanjing University of Chinese Medicine. The study was performed in accordance with the Declaration of Helsinki. The need for informed consent to participate was waived by the Ethics Committee of the Affiliated Hospital of Nanjing University of Chinese Medicine because of the retrospective nature of the study. All patient data were anonymized to maintain confidentiality throughout the research.

General Characteristics of the Participants and Definitions

The clinical, laboratory, and CT features of all the participants were collected. All of these data were retrospectively analyzed and retrieved from our institution's electronic medical records and picture archiving and communication system (PACS). Clinical parameters such as participants' age, sex, weight, height and body mass index (BMI) were collected. Laboratory information including the levels of serum alanine aminotransferase (ALT), albumin, creatinine, blood glucose, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), total cholesterol (TC) and triglyceride (TG) were obtained. Besides, the history of diabetes mellitus (DM) and chronic kidney disease (CKD) were also recorded. The definition of DM was based on the following situations: fasting plasma glucose levels on two separate occasions equal to or greater than 7.0 mmol/L or a prior medical history of DM. CKD was defined by a reduced glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 for over three months.

CT Features of the Participants

Non-contrast CT imaging was performed on a 256-slice clinically used CT scanner (iCT256, Philips, Hamburg, Germany). The CT imaging parameters were as follows: 120kVp, 50–80 mAs, collimation of 64 × 0.6 mm and pitch of 0.8. The mean CT radiation attenuation of bilateral erector spinae (ESRA) muscles and cross-sectional axial skeletal muscle (SMRA) at the medium level of the T11 vertebra were measured on axial CT images using ImageJ software. The identification criteria for CT images of skeletal muscle were −29 to +150 Hounsfield Units (HU) (Figure 2) as proposed

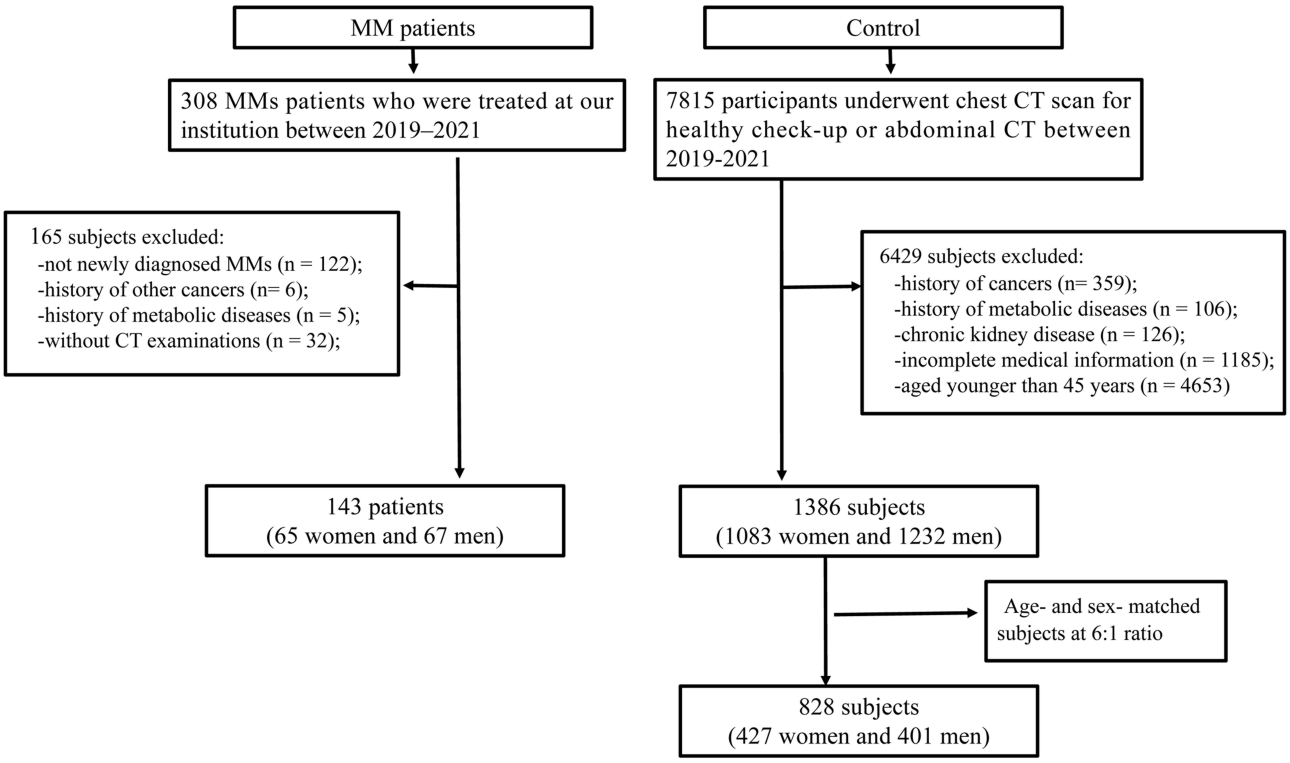

Figure 1 The flowchart for the inclusion of multiple myeloma (MM) patients and control subjects.

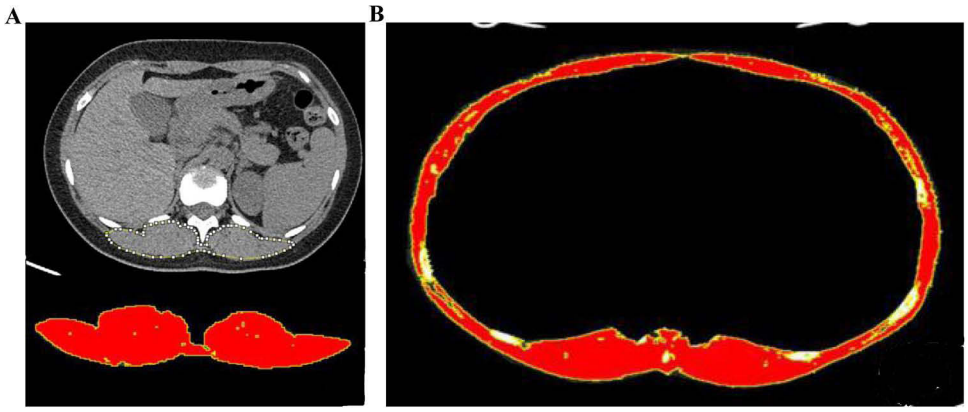

Figure 2 Illustrations of the measurements of computed tomography attenuation for bilateral erector spinae muscles (**A**) and cross-sectional axial skeletal muscle (**B**) at the medium level of the T11 vertebra.

in similar studies [20,21]. Muscle fat infiltration presence was defined using two separate metrics (1) T11 ESRA < 36 HU or (2) T11 SMRA < 34 HU. These cut-off points were chosen based on the lowest quartile of ESRA or SMRA of overall participants.

Statistical Analysis

The data obtained in this study were statistically analyzed via the SPSS 24.0 software package. Data for continuous variables were presented as the means ± standard deviations. Nominal variables were reported as count (%). Differences between groups were subsequently compared via independent-sample t tests, Mann–Whitney *U*-tests (continuous data), chi-square tests (qualitative data), or Fisher's exact tests (qualitative data). Multivariable logistic regression analyses were performed to assess the association between MM and the risk of low muscle CT attenuation while adjusting for the

selected variables, including age, sex and BMI (model 1), additional adjusting for liver function, renal function, diabetes, albumin (Model 2) and further adjusting for LDL-c, TG and HDL-c (Model 3). Receiver operating characteristic (ROC) curves were used to show the performance of the muscle CT attenuation in identifying MM. The area under the curve (AUC) was compared using Delong test. *P* values less than 0.05 were considered statistically significant.

Results

Characteristics of the Participants

A total of 966 participants were involved in this study. Table 1 shows their characteristics. The study was composed of 138 MM patients and 828 controls. ALT, creatinine, blood glucose, TG and the prevalence of diabetes or CKD in the MM group were significantly higher than those in controls. ($p < 0.001$). BMI, HDL-c, LDL-c, ESRA and SMRA in the MM group were significantly lower than those in controls ($p < 0.001$). In addition, significant differences were observed in weight ($p = 0.005$), albumin ($p = 0.001$) and TC ($p = 0.012$) between MM and controls. Low ESRA was observed in 256 participants (26.50%) and low SMRA was observed in 252 participants (26.08%). The prevalence of low ESRA and SMRA in MM patients were significantly higher than those in controls (66.7% vs 19.6%; 60.1% vs 20.4%, $p < 0.001$). No significant differences were observed in age, sex and height between MM and controls.

Muscle CT Attenuation Divided by Sex and Age Groups

Subsequently, we showed muscle CT attenuation in MM and control groups divided by sex (Figure 3) and age groups (40–60, 60–70, >70 years) (Figure 4). Figure 3 showed ESRA and SMRA in men and women in the MM and control groups. Muscle attenuation was significantly lower in MM group than in control group both in men and women

Table 1 Characteristics of the Subjects

	MM (n = 138)	Control (n = 828)	P value
Age (years)	64.75 ± 9.31	64.67 ± 14.09	0.95
Sex (men)	67 (48.55%)	401 (48.43%)	0.96
Weight (kg)	63.47 ± 11.92	66.39 ± 11.35	0.005
Height (cm)	164.32 ± 7.79	164.85 ± 8.70	0.51
BMI (kg/m^2)	23.42 ± 3.65	24.34 ± 3.06	< 0.001
ALT (U/L)	24.73 ± 17.53	22.89 ± 19.79	< 0.001
Albumin (mmol/L)	36.52 ± 6.09	44.20 ± 2.63	0.001
Creatinine (mmol/L)	103.02 ± 94.40	70.06 ± 28.98	< 0.001
Blood glucose (mmol/L)	5.59 ± 1.72	5.05 ± 1.70	< 0.001
HDL-c (mmol/L)	1.25 ± 0.64	1.50 ± 0.34	< 0.001
LDL-c (mmol/L)	2.21 ± 0.98	2.68 ± 0.76	< 0.001
TC (mmol/L)	4.00 ± 1.43	5.06 ± 1.06	0.012
TG (mmol/L)	1.70 ± 1.16	1.43 ± 1.18	< 0.001
Diabetes	31 (22.46%)	42 (5.07%)	< 0.001
CKD	16 (11.59%)	4 (0.48%)	< 0.001
T11 ESRA (HU)	32.26 ± 8.35	43.10 ± 8.16	< 0.001
T11 SMRA (HU)	32.11 ± 6.34	39.60 ± 6.76	< 0.001
Low T11 ESRA	92 (66.67%)	164 (19.81%)	< 0.001
Low T11 SMRA	83 (60.14%)	169 (20.41%)	< 0.001

Notes: Data for continuous variables were presented as the means ± standard deviations. Nominal variables were reported as count (%). Independent-sample t tests, Mann–Whitney *U*-tests (ALT and creatinine), chi–square tests (qualitative data) or Fisher's exact tests (CKD) were used for statistical analyses.

Abbreviations: ALT, Alanine aminotransferase; BMI, body mass index; CKD, chronic kidney disease; T11 ESRA, mean CT radiation attenuation of bilateral erector spinae muscles at the medium level of the T11 vertebra; HDL-c, high-density lipoprotein cholesterol; HU: Hounsfield Unit; LDL-c, low-density lipoprotein cholesterol; T11 SMRA, mean CT radiation attenuation of cross-sectional axial skeletal muscle at the medium level of the T11 vertebra; TC, total cholesterol; TG, triglyceride.

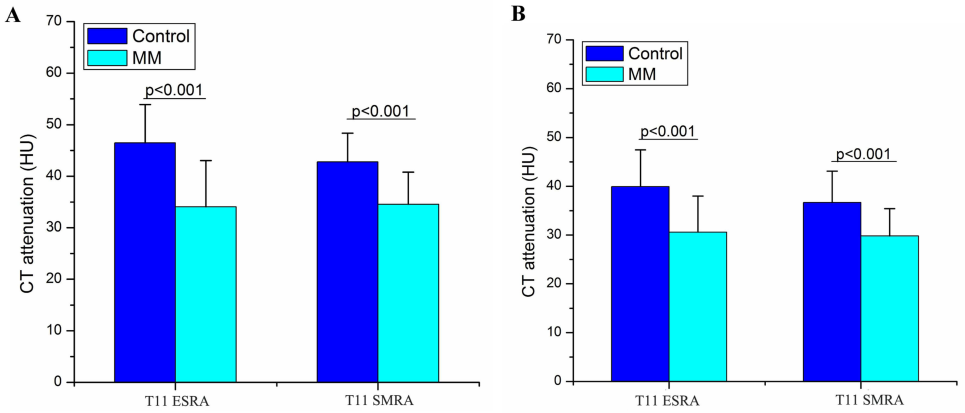

Figure 3 Mean muscle computed tomography attenuation between multiple myeloma (MM) patients and control in men (**A**) and women (**B**). T11 ESRA: mean CT radiation attenuation of bilateral erector spinae muscles at the medium level of the T11 vertebra; T11 SMRA: mean CT radiation attenuation of cross-sectional axial skeletal muscle at the medium level of the T11 vertebra.

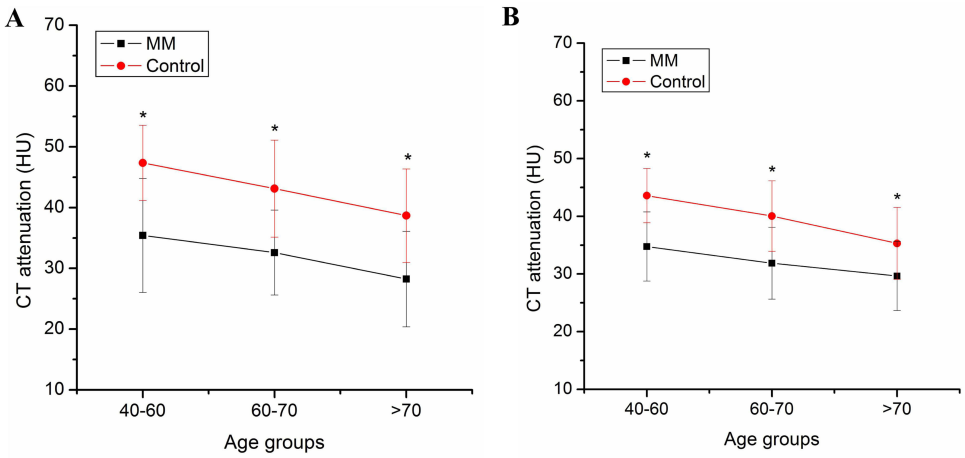

Figure 4 Muscle computed tomography attenuation between multiple myeloma (MM) patients and control in different age groups. (**A**) mean computed tomography (CT) radiation attenuation of bilateral erector spinae muscles at the medium level of the T11 vertebra (T11 ESRA); (**B**) mean CT radiation attenuation of cross-sectional axial skeletal muscle at the medium level of the T11 vertebra (T11 SMRA). * $p < 0.001$.

($p < 0.001$). Muscle CT attenuation all decreased with age in both MM and control groups (Figure 4). The muscle attenuation values in the MM group were lower than those in the control group across all age categories (all $p < 0.001$).

The Association Between MM and the Risk of Low Muscle Attenuation

Table 2 showed the associations between MM and the risk of low muscle attenuation by using logistic regression analysis. MM was significantly associated with the risk of low ESRA (odds ratio (OR) = 14.94, 95% confidence interval (CI): 9.33–23.91; OR = 11.39, 95% CI: 6.16–21.08; OR = 15.11, 95% CI: 7.76–29.39) and low SMRA (OR = 17.64, 95% CI: 10.41–29.89; OR =11.80, 95% CI: 5.99–23.25; OR = 12.00, 95% CI: 5.91–24.39) in all three models (model 1: age, sex and BMI; model 2: additional adjusting for liver function, renal function, diabetes, albumin; model 3: further adjusted for low-density lipoprotein cholesterol, triglyceride and high-density lipoprotein cholesterol). Age, BMI and sex were also significantly associated with the risk of low SMRA in these three models ($p < 0.001$). Similar results were observed in subjects with low ESRA except BMI (OR = 1.03, 95% CI: 0.98–1.10; OR = 1.04, 95% CI: 0.98–1.10; OR = 1.05, 95% CI: 0.99–1.11).

Subgroup Analyses

We investigated whether sex affected the association between the MM and the risk of low muscle attenuation by subgroup analyses (Table 3). Significant associations were found between the MM and the risk of low ESRA in men (OR

Table 2 Multivariable Logistic Regression Shown the Association Between MM and the Risk of Low Muscle Attenuation

		Model 1	p	Model 2	p	Model 3	p
		OR (95% CI)		OR (95% CI)		OR (95% CI)	
T11 ESRA < 36	Age	1.09 (1.07–1.11)	< 0.001	1.08 (1.07–1.10)	< 0.001	1.09 (1.07–1.10)	< 0.001
	BMI	1.03 (0.98–1.10)	0.18	1.04 (0.98–1.10)	0.19	1.05 (0.99–1.11)	0.13
	Sex (women vs men)	3.60 (2.51–5.19)	< 0.001	3.48 (2.40–5.05)	< 0.001	3.87 (2.63–5.69)	< 0.001
	MM (yes)	14.94 (9.33–23.91)	< 0.001	11.39 (6.16–21.08)	< 0.001	15.11 (7.76–29.39)	< 0.001
T11 SMRA < 34	Age	1.12 (1.10–1.14)	< 0.001	1.11 (1.09–1.13)	< 0.001	1.11 (1.09–1.14)	< 0.001
	BMI	1.15 (1.08–1.22)	< 0.001	1.16 (1.09–1.24)	< 0.001	1.16 (1.09–1.24)	< 0.001
	Sex (women vs men)	8.72 (5.74–13.26)	< 0.001	8.60 (5.58–13.24)	< 0.001	9.38 (6.00–14.68)	< 0.001
	MM (yes)	17.64 (10.41–29.89)	< 0.001	11.80 (5.99–23.25)	< 0.001	12.00 (5.91–24.39)	< 0.001

Notes: Model 2 was further adjusted for liver function, renal function, diabetes, albumin. Model 3 was further adjusted for low-density lipoprotein cholesterol, triglyceride and high-density lipoprotein cholesterol.

Abbreviations: BMI, body mass index; CI, confidence interval; CT, computed tomography; T11 ESRA, mean CT radiation attenuation of bilateral erector spinae muscles at the medium level of the T11 vertebra; OR, odds ratio; T11 SMRA, mean CT radiation attenuation of cross-sectional axial skeletal muscle at the medium level of the T11 vertebra.

Table 3 Subgroup Analyses to Show the Association Between the MM and the Risk of Low Muscle Attenuation Divided by Sex Using Multivariable Logistic Regression

			Model 1	p	Model 2	p	Model 3	p
			OR (95% CI)		OR (95% CI)		OR (95% CI)	
T11 ESRA	Men	Age	1.10 (1.06–1.13)	< 0.001	1.09 (1.06–1.12)	< 0.001	1.09 (1.06–1.13)	< 0.001
		BMI	1.01 (0.92–1.11)	0.18	1.01 (0.92–1.12)	0.73	1.03 (0.93–1.13)	0.13
		MM (yes)	20.65 (10.14–42.06)	< 0.001	10.07 (3.87–26.16)	< 0.001	12.18 (4.24–35.00)	< 0.001
	Women	Age	1.09 (1.06–1.11)	< 0.001	1.09 (1.06–1.11)	< 0.001	1.09 (1.06–1.10)	< 0.001
		BMI	1.06 (0.99–1.13)	0.10	1.06 (0.99–1.13)	0.11	1.06 (0.99–1.13)	0.11
		MM (yes)	10.85 (5.79–20.32)	< 0.001	14.03 (6.12–32.17)	< 0.001	19.16 (7.77–47.29)	< 0.001
T11 SMRA	Men	Age	1.13 (1.09–1.18)	< 0.001	1.12 (1.08–1.17)	< 0.001	1.13 (1.08–1.18)	< 0.001
		BMI	1.16 (1.04–1.29)	<0.001	1.20 (1.06–1.35)	0.003	1.20 (1.06–1.35)	0.004
		MM (yes)	31.99 (13.26–77.17)	< 0.001	11.73(3.74–36.78)	< 0.001	11.34 (3.32–38.77)	< 0.001
T11 SMRA	Women	Age	1.11 (1.09–1.14)	< 0.001	1.11 (1.09–1.14)	< 0.001	1.11 (1.09–1.14)	< 0.001
		BMI	1.15 (1.07–1.24)	<0.001	1.16 (1.08–1.25)	<0.001	1.16 (1.08–1.25)	<0.001
		MM (yes)	11.39 (5.86–22.13)	< 0.001	13.54 (5.70–32.20)	< 0.001	13.16 (5.32–32.57)	< 0.001

Notes: Model 2 was further adjusted for liver function, renal function, diabetes, albumin. Model 3 was further adjusted for low-density lipoprotein cholesterol, triglyceride and high-density lipoprotein cholesterol.

Abbreviations: BMI, body mass index; CI, confidence interval; CT, computed tomography; T11 ESRA, mean CT radiation attenuation of bilateral erector spinae muscles at the medium level of the T11 vertebra; OR, odds ratio; T11 SMRA, mean CT radiation attenuation of cross-sectional axial skeletal muscle at the medium level of the T11 vertebra.

= 20.65, 95% CI: 10.14–42.06; OR = 10.07, 95% CI: 3.87–26.16; OR = 12.18, 95% CI: 4.24–35.00) and women (OR = 10.85, 95% CI: 5.79–20.32; OR = 14.03, 95% CI: 6.12–32.17; OR = 19.16, 95% CI: 7.77–47.29) in the three models. Similarly, the MM was significantly associated with the risk of low SMRA in these three models ($p < 0.001$).

Role of Muscle CT Attenuation in Identifying MM

As shown in Figure 5, ROC curves were plotted to investigate the performance of the muscle CT attenuation in identifying MM. The results showed that the AUC was 0.827 for ESRA and 0.790 for SMRA. ESRA had a better performance than SMRA ($p < 0.01$).

Discussion

Musculoskeletal degeneration has been widely reported in various clinical diseases. The evaluation of skeletal muscle mass in patients with malignant tumors has garnered increasing attention in particular.[20,21] Sarcopenia, defining as

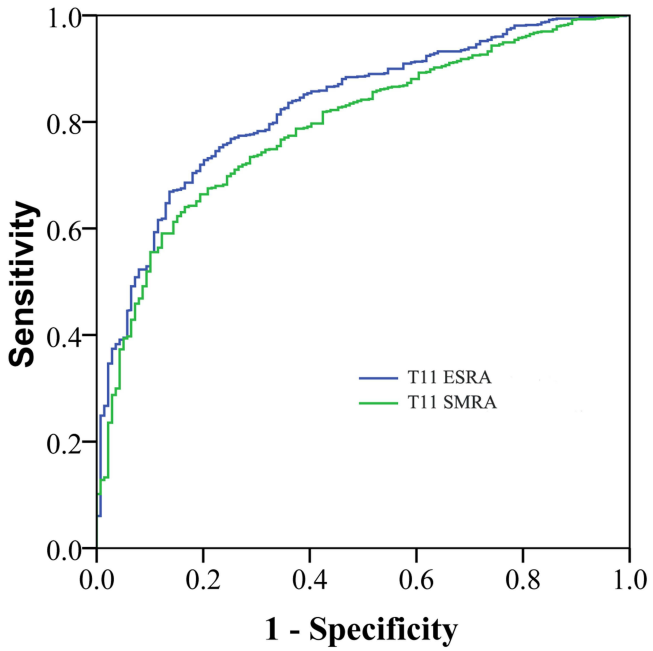

Figure 5 Receiver operating characteristic (ROC) curve demonstrated the performance of the muscle computed tomography (CT) attenuation in identifying multiple myeloma. Area under the curve was 0.827 for mean CT radiation attenuation of bilateral erector spinae muscles at the medium level of the T11 vertebra (T11 ESRA) and 0.790 for CT radiation attenuation of cross-sectional axial skeletal muscle at the medium level of the T11 vertebra (T11 SMRA).

a progressive loss of skeletal muscle mass, strength, and function, is fairly prevalent in many tumor patients, including MM.[22–24] However, due to the inconsistent findings on the impact of sarcopenia in MM, we employed muscle fat infiltration as a vehicle to asses musculoskeletal degeneration.[14,15] In the present study, we investigated the association between Muscle fat infiltration and MM by measuring the muscle attenuation on CT images and explored whether muscle density can serve as a risk factor for MM and comparing with the clinical and laboratory indicators. Our results showed that MM patients tended to have a lower muscle CT attenuation than that in control groups. The prevalence of low muscle CT attenuation was higher in MM patients than that in controls. Furthermore, our findings also indicated that MM was significantly associated with the risk of low muscle CT attenuation. A decrease in muscle CT attenuation had a acceptable performance in identifying MM.

Patients with tumor burden usually had a bad nutritional status and physical activity, leading to decreased muscle mass. Interestingly, muscle fat infiltration has emerged as a more precise indicator for assessing body composition in MM patients by measuring skeletal muscle radiodensity.[24,25] Muscle fat infiltration reflects fat accumulation within muscle tissue, reducing muscle quality and function.[25] It may be more sensitive than muscle mass or skeletal muscle area in identifying muscle degradation.[26] Although the prevalence of sarcopenia in hematologic malignancies is well documented,[1] how MM contributes to muscle fat infiltration is not fully understood. Potential mechanisms include the secretion of inflammatory factors by MM tumor cells, which may disrupt muscle protein synthesis and promote intramuscular fat accumulation.[27]

Studies showed that sarcopenia played an important role in the prognosis of cancer patients.[8] However, the relationship between muscle fat infiltration and hematologic malignancies remains unclear. A recent study found that over half of MM patients had low muscle radiodensity.[19] Interestingly, with the progression of the tumor, muscle radiodensity decreased significantly which led to a poorer survival.[19] Our study conducted a similar result of the prevalence of muscle fat infiltration in MM patients. Additionally, we discussed the cause of muscle fat infiltration between groups adjusted by patients' age because an advanced age may also lead to muscle degradation. Our results showed that a decreasing muscle CT attenuation was more commonly seen in elder participants. The reason might be that elders often experienced reduced muscle mass due to factors such as decreased protein synthesis capacity, inadequate protein intake, reduced physical activity or mobility, weakened

neuromuscular regulation, and abnormal conditions like diabetes.[28,29] Although muscle CT attenuation decreased with age in both groups, MM patients had lower values than controls across all age categories.

Consistent with previous reports, we found that the prevalence of diabetes and renal dysfunction in MM patients was significantly higher than those in control. Renal dysfunction has been regarded as one of the critical clinical features of MM.[10,11] An association between diabetes and haematological malignancies or MM has also been reported.[30–32] Moreover, our results showed that muscle CT attenuation has good performance in distinguishing MM from controls with AUC values between 0.79 and 0.83. Our data indicated that muscle CT attenuation may play some roles in MM diagnosis.

This study has several advantages. Our study may be the first one to report the prevalence and association between muscle fat infiltration and MM in China. This study also evaluated the impact of muscle fat infiltration in different age and sex group for the first time. However, there are several limitations in our study. First, the sample size is relatively small, particularly for MM patients. Second, although we considered some confounders, diet, physical exercise and alcohol habits were not controlled. Third, muscle fat infiltration was assessed by CT rather than magnetic resonance imaging (MRI), which is considered the good standard method for fat quantification. Furthermore, the relationship between muscle fat infiltration and MM prognosis requires further investigation. Our study is a retrospective study. We did not have the data of prognosis. Further investigations are needed to evaluate the prognostic value of muscle fat infiltration in MM patients.

Conclusions

In summary, our study revealed that muscle fat infiltration was more common in MM patients compared with control group. MM was significantly associated with the high risk of muscle fat infiltration. Muscle fat infiltration has acceptable performance in identifying MM. Muscle fat infiltration may be a useful marker for MM management.

Data Sharing Statement

All the data generated or analyzed and methods during this study are available from the corresponding author (Xiao Chen) upon reasonable request.

Ethical Approval and Consent to Participate

Ethics approval was obtained from the Affiliated Hospital of Nanjing University of Chinese Medicine. The study was performed in accordance with the Declaration of Helsinki. The need for informed consent to participate was waived by the Ethics Committee of the Affiliated Hospital of Nanjing University of Chinese Medicine because of the retrospective nature of the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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