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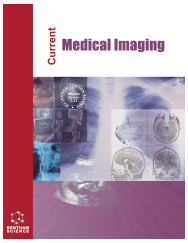

RESEARCH ARTICLE

Implication of Bone Mineral Density and Body Composition Parameters for Length of Hospital Stay in Patients with COVID-19

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Abstract:

Background:

Multisystem information, including musculoskeletal information, can be captured from chest CT scans of patients with COVID-19 without further examination.

Aims:

This study aims to assess the relationship between chest CT-extracted baseline bone mineral density (BMD) and body composition parameters and the length of hospital stay in these patients.

Methods:

A retrospective analysis was performed in a cohort of 88 patients with COVID-19. Correlation analysis and a generalized linear model (GLM) were used to assess the associations between the length of hospital stay and covariates, including age, sex, body mass index (BMI), BMD and body composition variables.

Results:

The mean length of hospital stay was 27.4±8.7 days. The length of hospital stay was significantly positively associated with age (r=0.202, p=0.046) and the paraspinal muscle fat ratio (r=0.246, p=0.021). The GLM involving age, sex, BMD, paraspinal muscle fat ratio, subcutaneous adipose tissue (SAT) area, visceral adipose tissue (VAT) area, and liver fat fraction (LFF) showed that the length of hospital stay was positively correlated with VAT area (β coefficients, 95% CI: 9.304, 1.141-17.478, p=0.025).

Conclusion:

The musculoskeletal features extracted from chest CT correlated with the prognosis of COVID-19 patients. Factors including old age, a higher paraspinal muscle fat ratio and a larger VAT area in patients with COVID-19 were associated with longer hospital stays.

Keywords: COVID-19, Bone density, Body composition, Subcutaneous fat, Visceral fat, CT scan.

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1. INTRODUCTION

Since December 2019, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global public

health disaster. According to data from the World Health Organization report of November 18, 2022, there have been over 633 million confirmed cases of COVID-19 worldwide, including over 6.5 million deaths [1]. For the diagnosis of COVID-19, reverse-transcription polymerase chain reaction (RT-PCR) is considered to be the gold standard [2]. In addition, unenhanced chest computed tomography (CT) is another sensitive diagnostic tool for detecting COVID-19 early and determining the stage of the disease [3].

On the other hand, unenhanced chest CT also provides a quick way to assess changes in pulmonary involvement and pneumonia for differential diagnosis [4]. For this reason, many studies have paid attention to the use of chest CT for the detection and quantification of COVID-19 pulmonary involvement [5]. Additionally, the association between chest CT manifestations and the prognosis of COVID-19 has received increasing attention. Pulmonary characteristics, including lesion area, volume, morphology and density, may be associated with the progression and prognosis of COVID-19 [6]. Since COVID-19 is a disease involving multiple systems, in addition to the respiratory system, other systems, including the nervous, cardiovascular, digestive, musculoskeletal and immune systems, have also been affected [7 - 10]. Moreover, multisystem information can be captured from chest CT without further examination and additional examination. Therefore, the association between extrapulmonary changes extracted on chest CT and COVID-19 prognosis deserves further attention.

Both bone and body composition parameters, including bone mineral density (BMD) and characteristics of muscle and adipose tissue, are obviously affected by COVID-19 [11 - 13]. During the pandemic, the long home quarantine caused a decrease in outdoor sun time, which resulted in difficulty in obtaining vitamin D and calcium [14]. Moreover, the lack of physical activities and exercise, increased sedentary behaviors, increased snacking frequency and alcohol intake caused by longer indoor times lead to increased weight and body mass index (BMI) [15, 16]. These changes are all crucial factors associated with musculoskeletal health. Therefore, the relationships between musculoskeletal parameters and COVID-19 prognosis deserve more attention. This study hypothesizes that there are associations between musculoskeletal parameters (such as BMD and factors related to muscle and adipose tissue) and COVID-19 prognosis, which is expressed by the length of hospital stay.

This study aims to assess the impact of baseline BMD and body composition parameters on the length of hospital stay in patients with COVID-19. This is the first study to assess the relationships between the musculoskeletal system (including BMD and body composition) and the length of hospital stay in hospitalized Chinese COVID-19 patients.

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2. METHODS

2.1. Study Design and Population

A retrospective chart review was performed of adult inpatients receiving medical care for COVID-19 at the Infectious Diseases Department of Beijing Ditan Hospital between January 2020 and February 2021. All patients underwent a throat swab examination when they were hospitalized. The patients whose RT-PCR tests were positive for SARS-CoV-2 were confirmed to have a diagnosis of COVID-19. Patients were eligible for inclusion if they had a diagnosis of COVID-19 and had obtained a chest CT scan, the range of which included at least the vertebral body of L2, within 7 days of admission to the infectious diseases department. Patients were excluded from the study if they had any of the following conditions: (1) vertebral fracture of L1 or L2; (2) vertebral deformity, inflammation, tumor or orthopedic operation history related to L1 or L2; or (3) poor-quality CT images (Fig. **1**). This study was reviewed and approved by the ethics committees of Beijing Friendship Hospital, Capital Medical University (2022-P2-216-01).

For each patient included, we obtained information from the medical record regarding general demographic and clinical history, COVID diagnosis history, and chest CT information. Body mass index (BMI) was calculated as the ratio of weight in kilograms (kg) divided by height in squared meters. According to BMI categories of the Working Group on Obesity in China (WGOC), BMI < 18.5 kg/m^2 denotes low weight, 18.5 $kg/m^2 \leq$ BMI < 24 kg/m^2 denotes normal weight, 24 $kg/m^2 \leq$ BMI < 28 kg/m^2 denotes overweight and BMI $\geq$ 28 kg/m^2 denotes obesity [17].

2.2. Measures

2.2.1. Chest CT Protocol

All nonenhanced chest CT images were scanned by the same CT scanner (Emotion16, Siemens Medical Solutions). Both the CT and calibration phantom scan protocols included 120 cm table height, 120 kV, 130 mA, 1.0 mm thickness, 1.0 mm pitch, 50 cm × 50 cm scan field of view, and standard reconstruction. All BMD and body composition data analyses used chest CT images and the same QCT software (QCT PRO, version 4.2, Mindways Software, Inc.). The Mindways Model 4 CT phantom was used for calibration. This study involved only the postprocessing of existing CT datasets without any additional radiation involved.

2.2.2. BMD Measurement

In the China guideline for the diagnosis criteria of osteoporosis with QCT [18], at least two lumbar vertebrae of 1st (L1), 2nd (L2) and 3rd (L3) lumbar vertebrae were recommended as the BMD measurement regions of interest (ROIs) in the lumbar spine. In view of the inferior scan range of chest CT of COVID-19 patients, we choose the L1 and L2 as the ROIs of lumbar spine BMD measurement. The mean BMD was calculated using the values of the L1 and L2

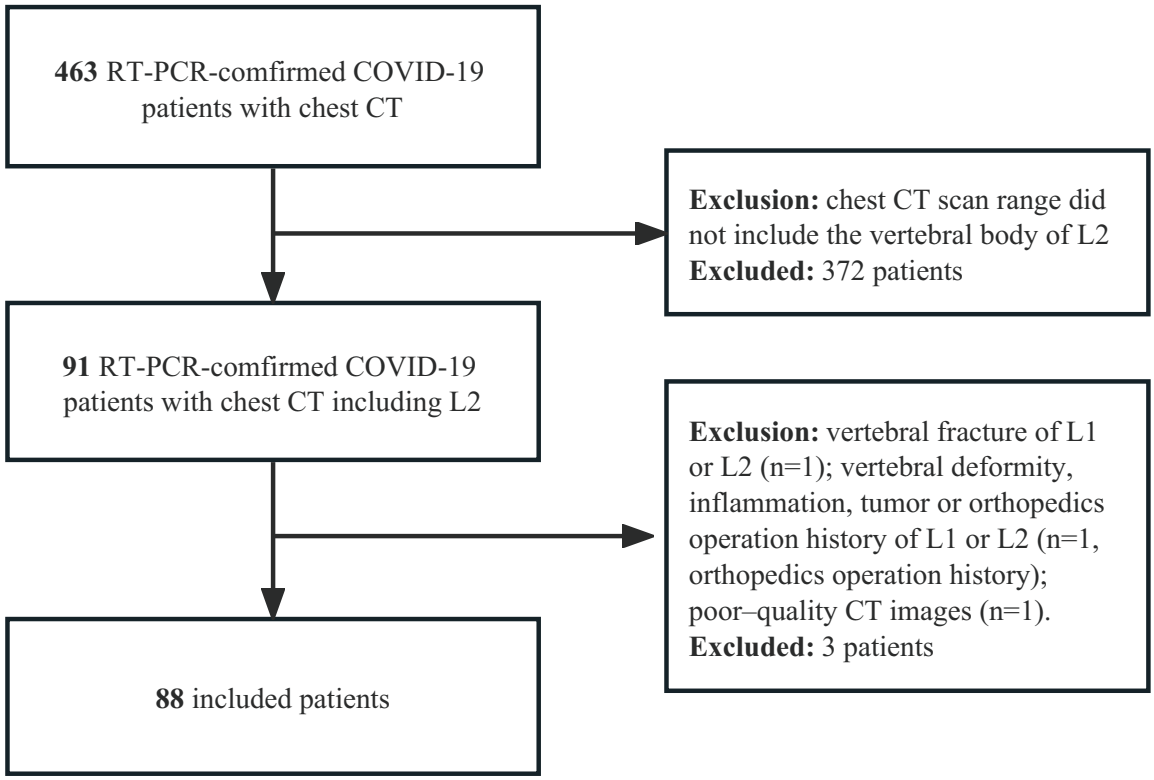


Fig. (1). Flowchart of 88 COVID-19 patients enrollment in the study population.
Note: RT-PCR, reverse-transcription polymerase chain reaction.

vertebrae. According to the China guideline for the diagnosis criteria of osteoporosis with QCT, a BMD >120 mg/cm^3 denotes normal BMD; a BMD between 80 mg/cm^3 and 120 mg/cm^3 denotes low bone density (or osteopenia), and a BMD <80 mg/cm^3 denotes osteoporosis [18].

2.2.3. Body Composition Measurement

The axial level of the mid-slice of the L1-L2 intervertebral disc was used to quantify the visceral adipose tissue (VAT) area and subcutaneous adipose tissue (SAT) area [19]. The same slice was used for paraspinal muscle area, paraspinal muscle fat area and liver fat fraction (LFF) measurement. The paraspinal muscle fat ratio (the paraspinal muscle fat area/paraspinal muscle area) was calculated and expressed as a percentage. The paraspinal muscle ROIs, including the erector spinae, were analyzed using the Auto Snake function in the Tissue Composition module of QCT software. The ROI for LFF determination was positioned in each of the liver Couinaud segments included in the image of the L1-L2 intervertebral disc level.

All QCT ROI measurements were performed by one trained radiologist (with 8 years of experience in QCT measurement) blinded to the general information of the population.

2.3. Statistical Analysis

The data normality was assessed by the Kolmogorov-Smirnov test. Descriptive statistics were reported as mean ± standard deviation for normally distributed data and median (interquartile range) for non-normally distributed data or frequencies. Pearson or Spearman correlation analysis and a generalized linear model (GLM) were performed to examine the associations between the length of hospital stay and covariates, including age, sex, BMI, BMD and body composition variables. For this GLM, the normality and homoscedasticity of the residuals were evaluated at first. The coefficient β and 95% confidence intervals (CI) were calculated in GLM. All statistical analyses were performed using the software package SPSS 22.0 (SPSS Inc.). P values <0.05 were considered statistically significant, and all p values were 2-sided.

3. RESULTS

3.1. Demographic Characteristics

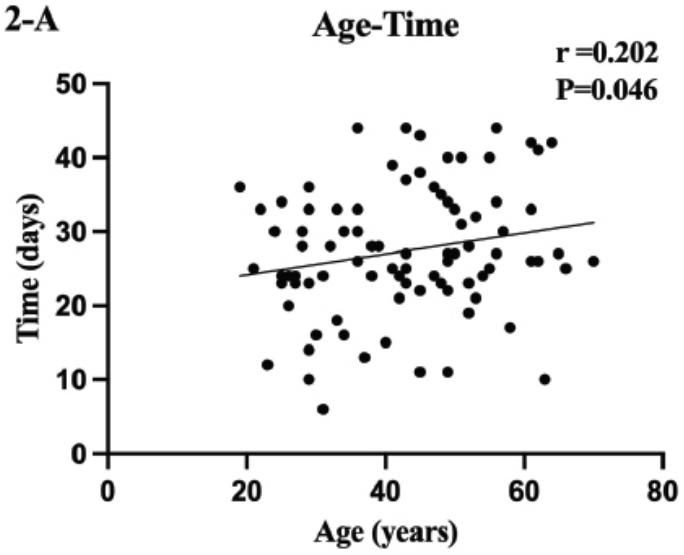
A total of 88 patients met the eligibility criteria for inclusion in this study. The demographic characteristics of the patients are detailed in Table **1**. There were 59 men (67.0%) and 29 women (33.0%). The mean age in the overall sample was 43.0±12.6 years (range 19-70 years), and the mean BMI was 24.7±3.7 kg/m2. Regarding BMI classification, the patients with normal BMI accounted for 36.4%. In this sample, 4.6%, 42.0%, and 17.0% of individuals were low-weight, overweight, and obese, respectively. The mean length of hospital stay was 27.4±8.7 days.

Table 1. Demographic, BMD and body composition characteristics of patients with COVID-19.

N	88
Age (years)	43.0±12.6
Gender, n (%) Male Female	 59 (67.0%) 29 (33.0%)
Height (cm)	167.8±8.2
Weight (kg)	70.0±12.9
BMI (kg/m^2) Low weight (<18.5) Normal weight (18.5~23.9) Overweight (24.0~27.9) Obese (≥28)	24.7±3.7 4 (4.6%) 32 (36.4%) 37 (42.0%) 15 (17.0%)
Length of Hospital Stay (days)	27.4±8.7
BMD (mg/cm^3) Normal BMD (>120) Low bone density (80~120) Osteoporosis (<80)	145.6±36.9 66 (75.0%) 20 (22.7%) 2 (2.3%)
Paraspinal muscle area (cm^2)	41.9 (16.6)
Paraspinal muscle fat area (cm^2)	1.7 (1.7)
Paraspinal muscle fat ratio (%)	3.5 (5.3)
SAT area (cm^2)	78.0 (64.4)
VAT area (cm^2)	122.2 (114.2)
LFF (%)	10.4 (5.8)

Note: The age, height, weight, BMI, length of hospital stay and BMD were expressed as mean ± standard deviation. The paraspinal muscle area, paraspinal muscle fat area, paraspinal muscle fat ratio, SAT area, VAT area and LFF were expressed as median (interquartile range). The gender, BMI categories, BMD categories were expressed as N (frequencies).

Abbreviations: BMI, body mass index; BMD, bone mineral density; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; LFF, liver fat fraction.



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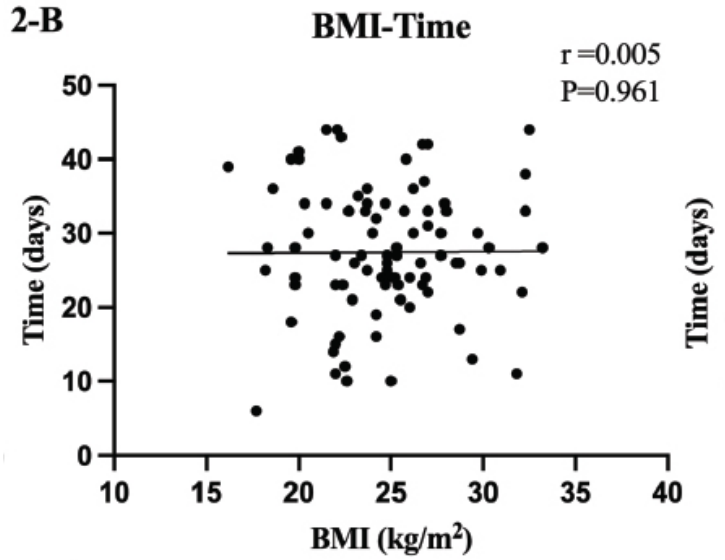
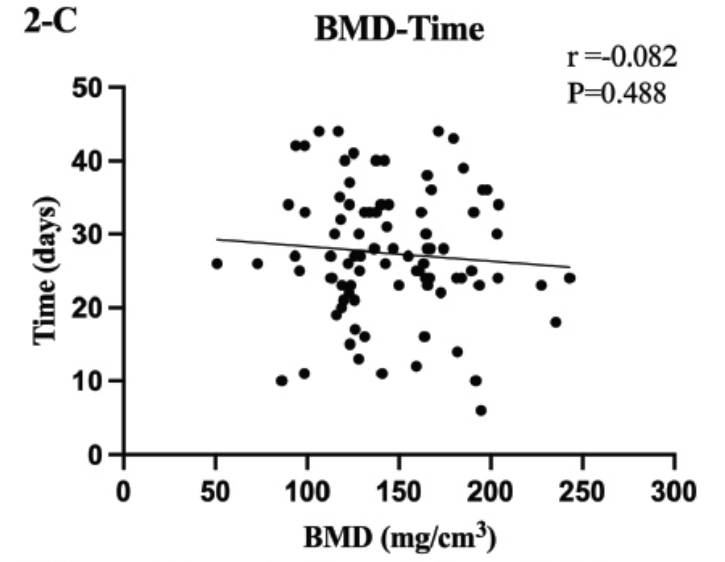

2-B
BMI-Time
r =0.005
P=0.961
Time (days)
BMI (kg/m²)


2-C
BMD-Time
r =-0.082
P=0.488
Time (days)
BMD (mg/cm³)

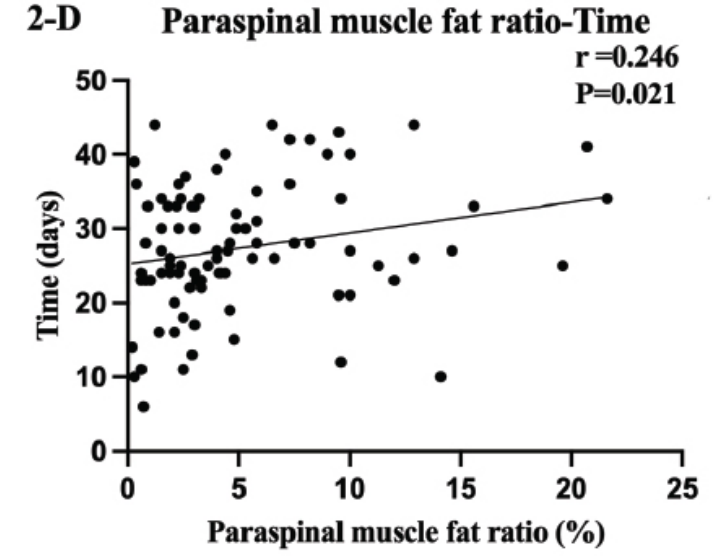

2-D
Paraspinal muscle fat ratio-Time
r =0.246
P=0.021
Time (days)
Paraspinal muscle fat ratio (%)

Fig. 2 contd.....

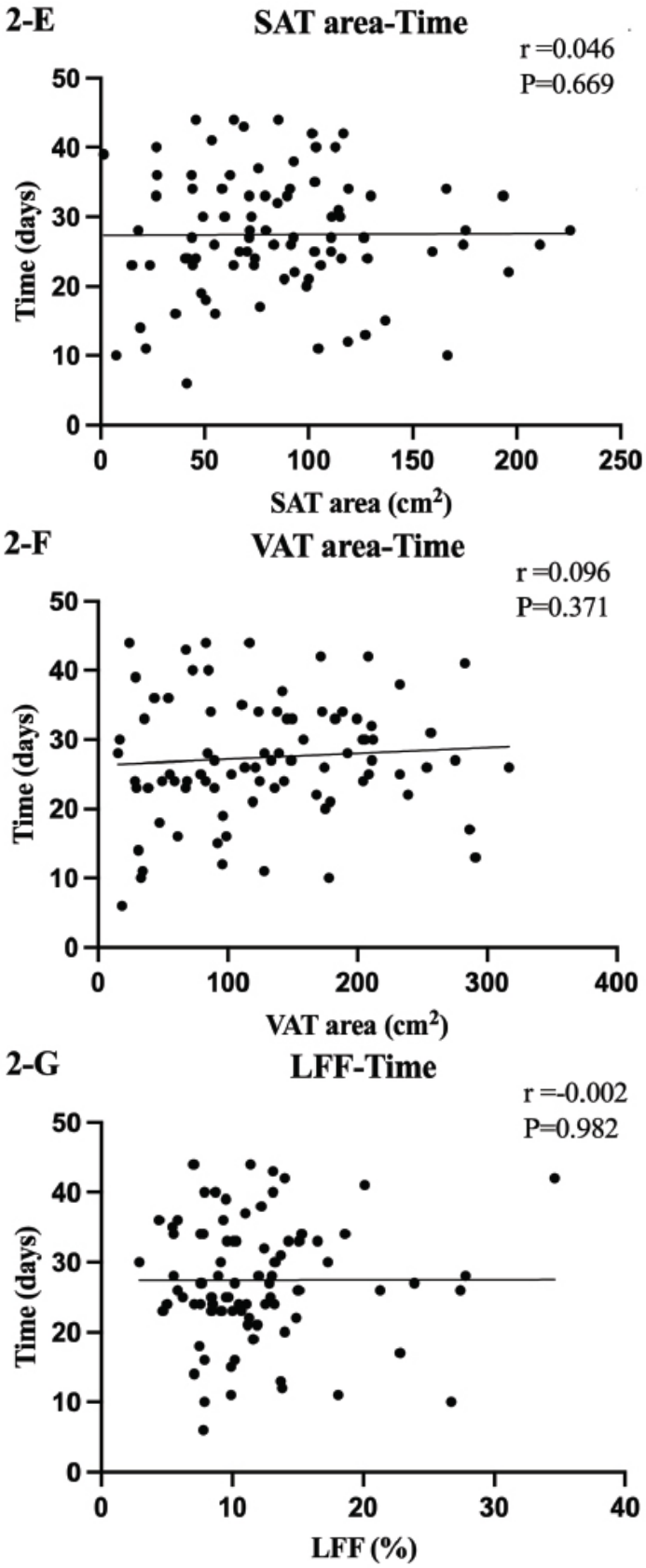


Fig. (2). Correlations between age (**2-A**), BMI (**2-B**), BMD (**2-C**), paraspinal muscle fat ratio (**2-D**), SAT area (**2-E**), VAT area (**2-F**), LFF (**2-G**) and the length of hospital stay in patients with COVID-19 (n=88).

3.2. BMD Characteristics

The mean BMD in the overall sample was 145.6±36.9 mg/cm^3 at the L1 and L2 lumbar vertebrae. The BMD of 66 patients (75.0%) was within the normal BMD range. Low bone density (or osteopenia) was diagnosed in 20 patients (22.7%), and only 2 patients (2.3%) had a BMD consistent with osteoporosis (Table **1**).

3.3. Body Composition Characteristics

The median areas of paraspinal muscle, paraspinal muscle fat, SAT and VAT were 41.9 cm^2, 1.7 cm^2, 78.0 cm^2 and 122.2 cm^2, respectively. The median paraspinal muscle fat ratio was 3.5%. The mean LFF was 10.4%.

3.4. Correlations between the Length of Hospital Stay and Age, BMI, BMD and Body Composition Variables

As shown in Fig. (**2**), the length of hospital stay was significantly positively associated with age (r=0.202, p=0.046) and the paraspinal muscle fat ratio (r=0.246, p=0.021). Correlation analyses revealed that the length of hospital stay was not correlated with BMI (r=0.005, p=0.961), BMD (r=-0.082, p=0.488), SAT area (r=0.046, p=0.669), VAT area (r=0.096, p=0.371) or LFF (r=-0.002, p=0.982).

3.5. Correlations between the Length of Hospital Stay and Multiple Variables in the GLM

The GLM included age, sex, BMD, paraspinal muscle fat ratio, SAT area, VAT area, and LFF. The model results are shown in Table **2**. In this model, the length of hospital stay was positively correlated with the VAT area (β coefficients, 95% CI: 9.304, 1.141-17.478; p=0.025). There was no correlative tendency between the length of hospital stay and age, BMD, paraspinal muscle fat area/muscle area ratio, SAT area, or LFF.

4. DISCUSSION

The severity and prognosis of COVID-19 depend on multisystem factors in addition to respiratory system-related variables. While chest CT provides information regarding pulmonary involvement, CT-extracted determinants from

Table 2. Generalized linear model (n=88) involving age, sex, BMD, paraspinal muscle fat ratio, SAT area, VAT area, and LFF for hospitalized patients with COVID-19.

	β coefficients	95% CI	P
Age			
19-39 ys	**Ref.**		**-**
40-59 ys	1.420	-3.100~5.940	0.538
60-70 ys	4.197	-4.911~13.305	0.366
Gender	-	-	-
Male	Ref.	-	-
Female	5.093	-0.269~10.455	0.063
BMD	-	-	-
Normal	Ref.	-	-
Low bone density	1.468	-3.539~6.476	0.565
Osteoporosis	9.531	-5.130~24.192	0.203
Paraspinal muscle fat ratio	-	-	-
P_{25}	Ref.	-	-
P_{50}	-0.801	-6.560~4.958	0.785
P_{75}	2.799	-4.606~10.203	0.459
P_{100}	0.929	-7.203~9.060	0.823
SAT area	-	-	-
P_{25}	Ref.	-	-
P_{50}	-1.701	-8.050~4.647	0.599
P_{75}	-2.512	-9.413~4.389	0.476
P_{100}	-7.241	-15.105~0.621	0.071
VAT area	-	-	-
P_{25}	Ref.	-	-
P_{50}	4.012	-2.375~10.398	0.218
P_{75}	6.097	-0.758~12.952	0.081
P_{100}	9.304	1.141~17.478	**0.025**
LFF	-	-	-
Normal	Ref.	-	-
Mild fatty liver	6.016	-3.835~15.867	0.231
Moderate and severe fatty liver	6.458	-4.921~17.837	0.266

Abbreviations: BMD, bone mineral density; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; LFF, liver fat fraction.

other systems, such as the musculoskeletal system, may also influence the progression and prognosis of COVID-19. As extrapulmonary features were extracted from chest CT directly, the collection of BMD and body composition information did not need further examination and required no additional examination. In our study, we found that musculoskeletal features extracted from chest CT impacted the prognosis of COVID-19. This study also showed that factors such as old age, high paraspinal muscle fat ratio and large L1-L2 VAT area were associated with longer hospital stays in patients with COVID-19.

4.1. The Impact of BMD on Prognosis in COVID-19 Patients

Since the outbreak of the pandemic, different studies have investigated the correlation between bone characteristics and COVID-19. However, the impacts of BMD on prognosis in COVID-19 patients remain controversial. Tahtabasi *et al*. [20] measured vertebral BMD in the bone window on axial chest CT images, and a vertebral BMD value less than 100 HU was defined as a lower BMD. In this study, vertebral BMD and lower BMD were both significant independent predictors of COVID-19 mortality. From a univariate logistic regression model including 58 patients, Kottlors *et al*. [21] reported that phantomless assessed T11-L1 BMD was a relevant prognostic predictor regarding the necessity of intensive care unit (ICU) treatment in the course of COVID-19 disease. However, in a multivariate regression analysis, including age, sex and other interaction factors in addition to BMD, it was a significant predictor. Vertebral fracture is one of the most serious results of osteoporosis, so Battisti *et al*. [22] evaluated vertebral fractures by sagittal image reconstruction from chest CT in a cohort of 239 COVID-19 and 262 non-COVID patients, and vertebral fractures were not significantly associated with mortality after age and gender adjustment in the COVID-19 group.

Notably, the average ages in the above studies were all more than 55 years. In our study, no correlation was found between BMD measured by QCT and the length of hospital stay of COVID-19 patients in univariate or multivariate analysis. However, a positive tendency was observed between lower BMD and longer length of hospital stay in both single- and multiple-factor analyses, even though it was not statistically significant. Potential explanations for this discrepancy include differences in the composition of the study population (a greater proportion of younger patients in our study), BMD measurement method (QCT images were used in our study) and race.

Some authors have hypothesized that because SARS-CoV-2 involves multiple systems during infection, there may be an association between increased mortality and fragility fractures or osteoporosis during this epidemic [23, 24]. On the other hand, the consequent longer home quarantine time and accompanying cessation of adequate medical care for patients with chronic diseases, including osteoporosis, also increased the mortality of COVID-19 patients [25].

4.2. The Impact of Body Composition on the Prognosis of COVID-19

For the body composition analysis, the results were inconsistent for the association between BMI, fat, muscle and COVID-19. Recent studies have shown that high BMI or obesity may be associated with an increased risk of more severe COVID-19 and higher mortality [26 - 28]. However, in our study, there was no association between BMI and length of hospital stay. The differences in the percentage of overweight and obese patients or the limited enrollment of our study may explain the discrepancy.

Even though dual-energy X-ray absorptiometry (DXA) is the gold standard for assessing body composition, CT can also be used for this assessment. The role of CT-derived muscle changes as a prognostic predictor in COVID-19 patients has also been discussed [29]. We found that the length of hospital stay in COVID-19 patients was significantly positively associated with the paraspinal muscle fat ratio ($r=0.246$, $p=0.021$). In hospitalized patients with COVID-19, lower paraspinal muscle mass at the level of the 5th thoracic vertebra on CT images correlated with incremental ICU admission and higher in-hospital mortality independently [30]. To evaluate the impact of sarcopenia on clinical outcomes in COVID-19 patients, a cohort study examined baseline sarcopenia, which was measured by the baseline skeletal muscle cross-sectional area from chest CT scans at the level of the 12th thoracic vertebra and revealed that baseline sarcopenia was independently correlated with longer hospital stays and tended to be associated with higher mortality in COVID-19 patients [31].

Among various body composition parameters, CT-derived VAT area has been shown to be a negative prognostic predictor in patients with COVID-19 [32, 33]. An increase in VAT area was associated with a higher risk of ICU treatment and an increased tendency to use mechanical ventilation applications [34]. In our study, a larger VAT area, but not SAT area, at the level of the L1-L2 intervertebral disc was a predictor of longer hospital stays in COVID-19 patients. Compared with CT-determined SAT, CT-determined VAT appears to be a more convincing marker of worse outcomes and increased mortality in patients with COVID-19, malignancies, metabolic diseases, pulmonary diseases and neurological diseases or who undergo surgery [29].

The present study had a few limitations. As COVID-19 is a sudden-onset infectious disease, it is difficult for a study to be designed prospectively. Therefore, this study has the following limitations. First, it must be stated that the BMD measurement range of QCT [18], which was at least at the height of L2, constrained the sample size in this study. Most chest CT scans cannot include the whole L1 vertebral body, not to mention L2. Only 19% of chest CTs included L2 in this cohort. The relatively small sample size limited our ability to perform BMD or body composition-related subgroup analyses. Moreover, because this study was a retrospective chart review, medical data regarding exercise, diet, and fracture risk factors, such as alcohol and smoking status, which could also affect health, were not collected systematically. However, given the dearth of studies exploring bone health and body composition

among COVID-19 patients, our findings are an important addition to the literature. In addition, given that the musculoskeletal system is an important system influencing body condition and health, explorations of its status have increased the power to detect potentially relevant associations between multifactor theory and the occurrence, process and prognosis of COVID-19. Further prospective multicenter studies of larger sample sizes investigating the mechanisms behind the association of bone health and body composition with COVID-19 are still needed.

CONCLUSION

We present the analysis of the relationships between BMD, body composition factors and the length of hospital stay among Chinese COVID-19 patients before medical treatment initiation. Factors including old age, high paraspinal muscle fat ratio and large VAT area were associated with longer hospital stays. The BMD and body composition parameters are feasibly reproducible and can be easily evaluated based on the chest CT images of COVID-19 patients without further examination and additional examination. Findings from exploring the relationship between BMD, body composition parameters and the clinical outcomes of patients with COVID-19 suggest that more attention should be given to elderly patients with advanced age, higher VAT and less muscle mass. These findings may help shed light on routine clinical practice due to their prognostic value. They may also be useful for the development of valuable epidemiological studies, mechanisms, and prevention strategies for reducing the length of hospital stay and saving precious medical resources in China.

LIST OF ABBREVIATIONS

COVID-19	=	Coronavirus disease 2019
RT-PCR	=	Reverse-transcription polymerase chain reaction
CT	=	Computed tomography
CI	=	Confidence interval
BMI	=	Body mass index
BMD	=	Bone mineral density
SAT	=	Subcutaneous adipose tissue
VAT	=	Visceral adipose tissue
LFF	=	Liver fat fraction

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethics committees of Beijing Friendship Hospital, Capital Medical University (2022-P2-216-01).

HUMAN AND ANIMAL RIGHTS

No animals were used in this study. All the human experiments were conducted in accordance with the Declaration of Helsinki (as revised in 2013).

CONSENT FOR PUBLICATION

The requirement for informed consent was waived due to the retrospective nature of the study.

STANDARD OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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