Association between sarcopenia and osteoporosis in chronic liver disease

Running title: Sarcopenia and osteoporosis in liver disease

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ABSTRACT

Aim: Sarcopenia and osteoporosis are important complications in chronic liver disease (CLD). The aim of this study was to investigate the relationship between sarcopenia and osteoporosis in patients with CLD.

Methods: We retrospectively investigated the relationship between sarcopenia and osteoporosis in 112 CLD patients (57 males and 55 females), including 40 cirrhotic patients (36%), by measuring the appendicular skeletal muscle mass index (ASMI) using bio-impedance analysis. Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry.

Results: The sarcopenia rate was 13% (14/112), and the osteoporosis and osteopenia rates were 17% (19/112) and 65% (73/112), respectively. The rate of osteoporosis was significant and high in patients with sarcopenia or cirrhosis. In linear regression analysis, sarcopenia was significantly associated with the BMD of the lumbar spine (Coefficient = -0.149, P = 0.014) and the femur neck (Coefficient = -0.110, P = 0.003). Cirrhosis was also significantly associated with low BMD of the lumbar spine (Coefficient = -0.160, P < 0.001) and the femur neck (Coefficient = -0.066, P = 0.015). In the logistic analysis, sarcopenia (odds ratio = 6.16, P = 0.039)

and cirrhosis (odds ratio = 15.8, P = 0.002) were independent risk factors for osteoporosis. The ASMI cut-off values for osteoporosis were 7.33 kg/m² in males and 5.71 kg/m² in females.

Conclusions: Sarcopenia was closely associated with osteoporosis, and a low ASMI was a potential predictor of osteoporosis in CLD patients. Screening for BMD may be required to detect osteoporosis in cirrhotic patients.

Key words: chronic liver disease, cirrhosis, sarcopenia, osteoporosis

INTRODUCTION

Cirrhosis results from different mechanisms of liver injury by several chronic liver diseases (CLDs), such as alcoholism, viral hepatitis, nonalcoholic fatty liver disease (NAFLD) and autoimmune liver disease.[1] Various systemic abnormalities develop as the disease progresses.[2] Cardiopulmonary, endocrine, hematological, renal and bone diseases are seen in patients with a CLD. Among them, osteoporosis is an important and common complication of CLD.[3] Cholestasis and cirrhosis are well-known risk factors for osteoporosis in CLD patients. There was a 2-fold relative increase in the risk of bone fracture in patients with primary biliary cholangitis (PBC) compared with that in the general population. Osteoporosis and bone fracture are associated with frailty.[4-6] Frailty is a condition characterized by self-reported exhaustion, weakness, slow walking speed, and low physical activity.[7] This condition is associated with mortality in patients with end-stage liver disease.[8] Early diagnosis and prevention of osteoporosis is needed in CLD patients.

Sarcopenia, which is defined as the loss of skeletal muscle mass and strength, is associated with complications and a worse prognosis in patients with CLD.[9] Sarcopenia is a predictor of minimal hepatic encephalopathy and mortality in patients

with cirrhosis.[10, 11] There was a significant association between sarcopenia and liver fibrosis in subjects with NAFLD.[12] In cirrhotic patients after liver transplantation, sarcopenia was a predictor of 1-year survival.[13] Sarcopenia closely correlates with the development of adverse events in patients with CLD. On the other hand, sarcopenia is associated with low bone mineral density (BMD) in patients with inflammatory bowel disease, chronic obstructive lung disease and healthy subjects.[14-16] Although handgrip strength and low lean body mass measured by dual-energy X-ray absorptiometry (DEXA) are associated with low BMD in cirrhosis patients, the association between sarcopenia and osteoporosis in patients with CLD remains unclear.[17, 18] The aim of this study was to investigate the relationship between sarcopenia and osteoporosis in patients with CLD.

METHODS

Study design and patients

In this retrospective, cross-sectional study, we reviewed the clinical records of adult CLD patients who had their appendicular skeletal muscle mass index (ASMI)

measured using bio-impedance analysis (BIA) between September 2014 and November 2017 at the Department of Gastroenterology, Fukushima Medical University Hospital, Fukushima, Japan.

This study protocol was performed according to the ethical standards of the Declaration of Helsinki and was approved by the Ethics Committee of Fukushima Medical University School of Medicine. This study was performed in accordance with the relevant guidelines and regulations. This study was approved to use an opt-out consent method by the Ethics Committee of Fukushima Medical University School of Medicine. A website with additional information, including the opt-out consent, was established for the study.

Inclusion criteria were (i) the presence of CLD, (ii) the ASMI measured using BIA, and (iii) BMD measured using DEXA. The etiologies of CLD included alcoholic liver disease (daily alcohol intake exceeds 20 g in women or 30 g in men), hepatitis B infection (positive HBs antigen), hepatitis C infection (positive HCV antigen or HCV RNA), NAFLD (daily alcohol consumption lower than 20 g in women or 30 g in men) and autoimmune liver disease (autoimmune hepatitis, PBC).[19-23] The exclusion criteria were (i) no data on handgrip strength, (ii) use of bisphosphonates, (iii)

prolonged (over 3 months) use of an oral steroid (more than 5 mg) within 12 months, and (iv) the presence of an active malignancy. Cirrhosis was diagnosed based on laboratory tests, tissue stiffness by transient elastography, morphological assessment with imaging tools (ultrasonography, computed tomography or magnetic resonance imaging), and physical findings of cirrhosis or liver biopsy.[24-27]

Of the consecutive 393 CLD patients who had their ASMI measured at our department, 146 patients fulfilled the inclusion criteria. After 34 patients were excluded (19 patients had no data on handgrip strength, 2 patients used bisphosphonates, 11 patients used steroids, and 2 patients had a malignancy), a total of 112 patients were ultimately recruited for analysis.

Diagnosis of sarcopenia and osteoporosis

Sarcopenia was diagnosed using the Assessment Criteria for Sarcopenia in Liver Disease (1st edition) reported by the Working Group for the Creation of Sarcopenia Assessment Criteria in the Japan Society of Hepatology.[28] According to those criteria, sarcopenia was defined by low handgrip strength and a low ASMI. Handgrip strength was measured using a Smedley grip dynamometer (TTM, Tokyo, Japan); the cut-off

values for sarcopenia diagnosis were 26 kg for men and 18 kg for women. Muscle mass was measured by BIA (InBody770; Inbody Co., LTD, Seoul, Korea). The ASMI was calculated as the sum of skeletal muscle mass in the arms and legs divided by the square of height (kg/m^2); the cut-off values of the ASMI for sarcopenia diagnosis were 7.0 kg/m^2 for males and 5.7 kg/m^2 for females.

Osteoporosis, osteopenia, and normal BMD were diagnosed according to the World Health Organization criteria (osteoporosis: T-score ≤ -2.5; osteopenia: T-score between -2.5 and -1; normal BMD: T-score > -1).[29] BMD was measured at the lumbar spine (L2-L4) and the femur neck using DEXA (GE Healthcare Madison, WI. USA.). The young adult mean (YAM) (lumber spine: 20 to 44 years of age) was 1.19 g/cm^2 in males and 1.12 g/cm^2 in females. The YAM (femur neck) was 0.95 g/cm^2 in males and 0.90 g/cm^2 in females.

Clinical and laboratory assessment

Blood was obtained after overnight fasting. Serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, albumin, total bilirubin, creatinine, sodium, platelet count, prothrombin

time-international normalized ratio (PT-INR), bone alkaline phosphatase (BAP) and urine N-telopeptides of type I collagen (NTx) were examined using standard clinical methods (Department of Clinical Laboratory, Fukushima Medical University Hospital). The FIB-4 index was calculated according to published formulas.[30] Measurement of liver stiffness by transient elastography was performed using Fibroscan (EchoSens, Paris, France). We investigated known risk factors for osteoporosis, such as the presence of chronic kidney disease (eGFR < 60 mL/min/1.73 m^2) and diabetes mellitus (use of an oral hypoglycemic agent or insulin).[31, 32]

Statistical analysis

The clinical data are expressed as the median and 25th-75th interquartile ranges (IQR). The clinical data were compared between groups using the Mann-Whitney U test and the Kruskal-Wallis test. Differences in categorical variables were determined using Fisher's exact test. Correlations between the data were analyzed using Spearman's rank correlation test. Association BMD and the clinical data was analyzed using multivariate linear regression analysis. Univariate and multivariate logistic regression analyses were used to assess the predictors of osteoporosis. We applied

receiver operating characteristic (ROC) curve analysis to determine the ideal cut-off levels that could predict the diagnostic performance of osteopenia and osteoporosis. Differences of $P < 0.05$ were considered statistically significant. The data were analyzed using prism 7.0 software (GraphPad Software, Inc) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 3.2.1), and a modified version of R commander (version 2.1-7).[33]

RESULTS

Baseline characteristics

The baseline characteristics of the study participants are shown in Table 1. A total of 112 patients with CLD were recruited for the analysis. Among them, 57 were male, and 55 were female, with a median age of 65 (58-73) years. None of the patients had been diagnosed with hepatocellular carcinoma or any other malignancy, and none had ascites, peripheral edema or a history of fragility fractures. CLD patients predominantly had hepatitis C infection and NAFLD, and there were 40 patients with

cirrhosis (36%). Chronic kidney disease was identified in 22 patients (20%) and diabetes mellitus in 25 patients (22%). The median handgrip strength was 32 (29-40) kg in males and 21 (17-25) kg in females. The median interval period between measurements of the ASMI and BMD was 35 (0-91) days. The median ASMI measured using BIA was 7.70 (7.03-8.23) kg/m² in males and 6.06 (5.64-6.58) kg/m² in females, and 27 patients (24%) had an ASMI that was below the cut-off value. There were 14 patients with sarcopenia (13%); 5 patients were male, and 9 patients were female. The prevalence rates of osteopenia or osteoporosis (osteopenia/osteoporosis) for all patients, all males and all females were 73/112 (65%), 30/57 (52%) and 43/55 (78%), respectively. The prevalence rates of osteoporosis for all patients, all males and all females were 19/112 (17%), 6/57 (11%) and 13/55 (24%), respectively.

Comparison of the clinical characteristics of patients with and those without cirrhosis

Between patients with and those without cirrhosis (Table 2), significant differences were detected in PT-INR, albumin, FIB-4 index, and liver stiffness and in the

prevalence of osteoporosis (28% vs 11%, P = 0.036). There was no significant difference in the prevalence of sarcopenia.

Comparison of clinical characteristics among patients with normal BMD, osteopenia and osteoporosis

Among the normal BMD, osteopenia and osteoporosis groups, significant differences were detected in age, sex, BMI, handgrip strength, the ASMI, sarcopenia prevalence, the BMD of the lumbar spine and BMD of the femur neck (Table 3). Although there was no significant difference in the prevalence of cirrhosis, the rate of cirrhosis was 57% in patients with osteoporosis and 28% in those with a normal BMD.

Comparison of clinical characteristics between patients with and those without sarcopenia

We analyzed the association between sarcopenia and osteoporosis (Table 4). Between patients with and those without sarcopenia, there were significant differences in BMI, the BMD of the lumber spine, the BMD of the femur neck, the rate of osteopenia/osteoporosis (100% vs 60%, P = 0.002) and the rate of osteoporosis

(57% vs 11%, P < 0.001). The relationship among age, BMD, liver cirrhosis (LC) and sarcopenia is shown in Fig. 1. We classified patients into 4 groups according to the presence of LC and sarcopenia. The BMD of patients with sarcopenia was less than the YAM, regardless of age.

In male patients with CLD, significant differences were detected between the group with and without sarcopenia in BMI, the BMD of the lumbar spine, and the BMD of the femur neck. Although osteoporosis did not show a significant difference, 2 of 5 male patients with sarcopenia had osteoporosis, and all patients with sarcopenia had osteopenia. In female patients with CLD, significant differences were detected between the group with and without sarcopenia in BMI, the BMD of the lumbar spine, the BMD of the femur neck and osteoporosis.

Factors associated with osteoporosis in patients with CLD

We analyzed the association between BMD and the ASMI using multivariate linear regression analysis (Table 5). Age, female sex, BMI, the presence of cirrhosis, urine NTx and the presence of sarcopenia were analyzed as potential factors. In the lumbar spine, female sex (Coefficient = -0.190, P < 0.001), the presence of cirrhosis

(Coefficient = -0.160, P < 0.001), urine NTx (Coefficient = -0.002, P = 0.018) and the presence of sarcopenia (Coefficient = -0.149, P = 0.014) were significantly associated with BMD. In the femur neck, female sex (Coefficient = -0.125, P < 0.001), the presence of cirrhosis (Coefficient = -0.066, P = 0.015) and the presence of sarcopenia (Coefficient = -0.110, P = 0.003) were associated with BMD. There was a significant positive correlation between the ASMI and BMD of the lumbar spine and the femur neck, (lumbar spine: r = 0.44, P < 0.001, femur neck: r = 0.52, P < 0.001). The correlations between the ASMI and BMD are shown in Fig. 2. Handgrip strength was also significantly correlated with BMD (lumbar spine: r = 0.46, P < 0.001, femur neck: r = 0.49, P < 0.001).

Univariate and multivariate logistic regression analyses for factors associated with osteoporosis in CLD patients are shown in Table 6. Age, BMI, the presence of cirrhosis, urine NTx and the presence of sarcopenia were analyzed as potential factors. In patients with CLD, the univariate analysis identified the following factors as being significantly associated with osteoporosis: age, BMI, the presence of cirrhosis and the presence of sarcopenia. The multivariate analysis revealed that BMI [odds ratio (OR) = 0.73; 95% CI = 0.56-0.95; P = 0.021], the presence of cirrhosis (OR = 15.8; 95% CI

= 2.64-95.1; P = 0.002) and the presence of sarcopenia (OR = 6.16; 95% CI = 1.10-34.6; P = 0.039) were significantly associated with osteoporosis.

ROC curve analysis was performed to determine the optimal cut-off values for the ASMI to distinguish osteopenia or osteoporosis at the lumbar spine and femur neck (Fig. 3). The cut-off values of the ASMI for osteopenia were 7.587 kg/m² for male patients and 6.266 kg/m² for female patients. The area under the ROC curve, specificity and sensitivity for the ASMI for osteopenia were 0.656, 0.600 and 0.704, respectively, in male patients and 0.554, 0.605 and 0.538, respectively, in female patients. The cut-off values of the ASMI for osteoporosis were 7.336 kg/m² in male patients and 5.713 kg/m² in female patients. The area under the ROC curve, specificity and sensitivity for the ASMI for osteoporosis were 0.768, 0.833 and 0.725, respectively, in male patients and 0.718, 0.615 and 0.738, respectively, in female patients.

DISCUSSION

The present study demonstrated that sarcopenia and cirrhosis were independent risk factors for osteoporosis in patients with CLD. BMD of the lumbar spine and the

femur neck was significantly correlated with the ASMI measured using BIA. In the multivariate linear regression analysis, sarcopenia and cirrhosis were independently associated with low BMD of the lumber spine and femur neck. In the multivariate logistic regression analyses, sarcopenia and cirrhosis were independent risk factors for osteoporosis. The ASMI measured using BIA is a potential predictor of osteoporosis in CLD patients. Interestingly, the cut-off value of the ASMI for predicting osteoporosis in this study was similar to the cut-off value of the ASMI for sarcopenia.

Regarding the relationship between sarcopenia and osteoporosis, there are several reports on the association between bone and muscle. Muscle mass deficit was an independent risk factor for low BMD in healthy subjects.[34] Both lean mass and muscle strength were positively associated with BMD.[16] Sarcopenia was correlated with the BMD of patients with inflammatory bowel disease, chronic obstructive lung disease and healthy subjects.[14-16] Previous reports showed that low handgrip strength and low lean body mass were risk factors for low BMD in patients with cirrhosis.[17, 35] The biochemical communication between bone and muscle has been identified.[36, 37] Several molecules released by muscle and bone affect each

other, such as growth factors, myokines and osteokines, supporting the close association between osteoporosis and sarcopenia.

CLD is the one of the causes of secondary sarcopenia.[38] The prevalence of sarcopenia measured by BIA was 38% in Japanese patients with CLD.[28] Because osteoporosis can develop as sarcopenia progresses, the prevention and early diagnosis of osteoporosis in patients with CLD is very important. Handgrip strength has been proposed as a predictor of osteoporosis in cirrhotic patients.[17] Similar to a previous report, in this study, we showed that low handgrip strength was associated with low BMD and that handgrip strength was significantly lower in patients with osteoporosis than in patients with a normal BMD. Moreover, we showed that the ASMI measured by BIA showed a significant positive correlation with BMD. The ASMI might also be a potential predictive factor for diagnosing osteoporosis. Interestingly, the cut-off value of the ASMI for osteoporosis was almost the same as that for sarcopenia.[28] This result showed the importance of screening for osteoporosis in CLD patients who are suspected to have sarcopenia.

The multivariate analysis revealed that the presence of cirrhosis was significantly associated with low BMD and osteoporosis. It is known that the

prevalence of osteoporosis in the vertebrae is higher than that in the femoral bones (23% vs 5%) in patients with cirrhosis who are on liver transplantation lists.[39] Values of coefficient of cirrhosis in the multivariate linear regression analysis were -0.160 for the lumber spine and -0.066 for the femur neck. These results suggest that cirrhosis is associated with not only low BMD in the lumber spine but also low BMD in the femur neck, and the impact of cirrhosis for BMD is greater in the lumber spine than in the femur neck. Early screening for BMD might be needed to detect low BMD in the lumbar spine and femur neck in cirrhotic patients. In this study, cirrhosis was a risk factor of osteoporosis and low BMD. The osteoporosis rate of the cirrhosis group was significantly higher than that of the non-cirrhosis group (Table 2), but the BMD of the lumber spine and femur neck did not show significant differences. This difference in rate may be due to the different cut-off values of BMD for osteoporosis according to sex. The YAM of the lumber spine was 1.19 g/cm^2 in males and 1.12 g/cm^2 in females. The YAM of the femur neck was 0.95 g/cm^2 in males and 0.90 g/cm^2 in females. Although no significant difference was identified, more male patients were present in the cirrhosis groups than in the non-cirrhosis group. In the multivariate regression analysis including sex, cirrhosis was independently correlated with BMD.

The severity of cirrhosis among the patients in this study was relatively low. Most cirrhotic patients in this study exhibited compensated cirrhosis; only a few patients exhibited decompensated cirrhosis. Decompensated patients often have peripheral edema or ascites, which affects BIA methods. A study analyzing the factors related to BMD in patients with cirrhosis reported that in cirrhotic patients, the clinical severity of cirrhosis was not correlated with the BMD of the lumber spine or the femoral neck, and similarities in bone conditions were observed between compensated and decompensated patients with cirrhosis.[17] We demonstrated that liver cirrhosis was a risk factor of osteoporosis in patients with CLD, although most cirrhosis patients were in a compensated state. Our finding does not contradict previous reports. In addition, the FIB-4 index and liver stiffness by Fibroscan in this study were relatively low compared to reported cirrhosis cut-off values.[40, 41] Although we diagnosed cirrhosis based on clinical findings, we cannot deny that not only cirrhosis but also advanced fibrosis (such as METAVIR 3[42]) patients were included in the cirrhotic group. Regardless, the association between clinically diagnosed cirrhosis and osteoporosis in this study is important for patients with CLD.

A previous study showed that BMI and the Fibroscan value were significant independent risk factors for osteoporosis in cirrhotic patients.[43] The relationship between obesity and osteoporosis is complex. BMI was correlated with BMD; every unit increase in BMI was associated with an increase of 0.0082 g/cm^2 in BMD.[44] However, obesity was a risk factor for bone fracture when BMD was adjusted.[45] We showed that there is an association between BMI and osteoporosis in CLD patients, and the use of BMI as a predictive factor for bone fracture in patients with CLD should be considered. Fibroscan and the FIB-4 index are non-invasive methods for assessing liver stiffness[30, 46] and are useful for assessing the degree of liver insufficiency. We demonstrated that the presence of cirrhosis was associated with osteoporosis. However, the Fibroscan and FIB-4 index values did not show significant differences among the normal BMD, osteopenia and osteoporosis groups. In a previous study, the cut-off Fibroscan value for hepatic osteodystrophy (osteopenia and osteoporosis) was 60 kPa,[44] which is a relatively high value even in cirrhotic patients.[25] The association between liver stiffness and BMD may become clearer as liver insufficiency progresses.

We analyzed BAP and urine NTx as bone metabolic markers and found that BAP and urine NTx did not show significant differences among the cirrhosis, osteoporosis and sarcopenia groups in this study. BAP is associated with bone formation, and urine NTx is associated with bone resorption.[47, 48] The association between bone metabolic markers and CLD is not fully understood. Collagen-related markers of bone turnover, such as NTX, can reflect the severity of liver fibrosis, but these markers were not associated with osteopenia in patients with PBC.[49] The results of our study also suggest that levels of NTx are not associated with osteopenia or osteoporosis in patients with CLD. Thus, the association between liver fibrosis and collagen-related markers should be considered when assessing bone turnover using these markers.[49]

There have been some studies on the physiopathology of osteoporosis in patients with CLD. An imbalance between receptor activator of nuclear factor kβ ligand (RANKL) and osteoprotegerin (OPG) was shown to be related to bone loss.[50, 51] RANKL is crucial for osteoclastic activation and differentiation, and OPG is a RANKL receptor.[52] Soluble RANKL (sRANKL) and OPG levels were found to be higher in liver disease patients than in controls. The OPG/sRANKL ratio was

correlated with the degree of liver insufficiency, and it was higher in the group of cirrhotic patients with osteoporosis and osteopenia than in the group without osteoporosis and osteopenia.[53] This finding suggests that high sRANKL levels reflect an increase in bone turnover in liver disease patients and that the OPG/sRANKL ratio might reflect the maintenance of bone homeostasis.[54] Serum myostatin, a negative regulator of muscle protein synthesis, has been reported to be present at significantly higher levels in patients with cirrhosis than in healthy controls.[55, 56] Nishikawa et al. showed that serum myostatin levels were higher in cirrhotic patients with Child-Pugh B or C than in patients with Child-Pugh A.[9] Myostatin strongly accelerates RANKL-mediated osteoclast formation in vitro.[57] Elevated myostatin levels might be associated with osteoporosis in patients with CLD.

There were some limitations in this study. First, this is a single-center, retrospective study. Thus, a multicenter, prospective study is needed. Second, the number of patients included in this analysis was low. Although liver cirrhosis was associated with osteoporosis in this study, a larger sample size is needed to elucidate the correlation between osteoporosis and the degree of liver insufficiency.

Third, this study included several etiologies of CLD and both male and female patients. The prevalence and mechanism of osteoporosis in patients with different etiologies and sexes might be different. The results of past reports and this study have shown that there is a close association between sarcopenia and osteoporosis, which may differ for different disease etiologies and sexes.

CONCLUSION

In conclusion, we found an association between sarcopenia and osteoporosis in patients with CLD. The ASMI measured by BIA is a potential predictive factor not only for sarcopenia but also for osteoporosis in these patients. The presence of cirrhosis was associated with low BMD in the lumbar spine and femur neck as well as with osteoporosis. Our findings may be useful for the early diagnosis of osteoporosis in CLD patients. Further investigation is needed to assess the association between osteoporosis and sarcopenia in patients with CLD.

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Competing financial interests

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Table 1. Baseline characteristics of the study participants.

Variables	All	Male	Female	P
N	112	57	55	
Age, years	65 (58-73)	64 (58-72)	69 (62-76)	0.030
BMI	24.1 (21.2-27.6)	24.6 (21.1-28.2)	22.9 (21.4-27.4)	0.41
Etiology				
Hepatitis C	34 (30%)	17 (29%)	17 (30%)	1
Hepatitis B	14 (13%)	10 (18%)	4 (7%)	0.15
Alcohol	15 (13%)	13 (23%)	2 (3%)	0.004
NAFLD	27 (24%)	15 (26%)	12 (22%)	0.66
Autoimmune liver disease	22 (19%)	2 (3%)	20 (36%)	< 0.001
Diabetes mellitus	25 (22%)	14 (24%)	11 (20%)	0.65
Chronic kidney disease	22 (20%)	11 (19%)	11 (20%)	1
Cirrhosis	40 (36%)	23 (40%)	17 (30%)	0.32
Chronic hepatitis/Child A/Child B/Child C	72/30/8/2	34/16/6/1	38/14/2/1	0.24
Laboratory data				

Total bilirubin, mg/dL	0.8 (0.7-1.1)	0.9 (0.7-1.4)	0.8 (0.7-0.9)	0.018
Prothrombin time-INR	0.98 (0.94-1.04)	0.99 (0.94-1.06)	0.98 (0.94-1.01)	0.33
Serum albumin, g/dL	4.2 (3.8-4.2)	4.2 (3.9-4.5)	4.1 (3.8-4.3)	0.34
Serum creatinine, mg/dL	0.77 (0.65-0.97)	0.94 (0.78-1.10)	0.66 (0.60-0.75)	< 0.001
eGFR	64 (53-76)	59 (52-73)	66 (61-76)	0.063
AST, U/L	28 (21-44)	31 (22-47)	24 (21-34)	0.053
ALT, U/L	20 (15-35)	25 (17-46)	18 (15-26)	0.008
ALP, U/L	250 (196-338)	245 (193-359)	254 (198-328)	0.94
GGT, U/L	32 (20-66)	36 (23-73)	26 (17-53)	0.016
BAP, μg/L	15.3 (12.2-19.8)	14.7 (12.0-19.1)	15.4 (12.3-20.4)	0.72
Urine NTx, nmol/BCE/mmol Cr	29.4 (21.5-41.9)	24.4 (18.2-37.9)	36.7 (24.9-44.5)	0.012
FIB-4 index	2.41 (1.62-3.46)	2.04 (1.52-4.14)	2.53 (1.78-3.31)	0.62
Fibroscan, kPa	6.8 (5.3-10.2)	7.3 (5.7-10.4)	6.4 (4.9-10.1)	0.24
Handgrip strength, kg	26 (20-32)	32 (29-40)	21 (17-25)	< 0.001
ASMI, kg/m²	6.82 (5.95-7.78)	7.70 (7.03-8.23)	6.06 (5.64-6.58)	< 0.001
Sarcopenia	14 (13%)	5 (9%)	9 (16%)	0.26
BMD lumbar spine, g/cm²	1.09 (0.95-1.23)	1.20 (1.07-1.28)	0.99 (0.87-1.12)	< 0.001

BMD femur neck, g/cm²	0.78 (0.70-0.87)	0.84 (0.78-0.95)	0.72 (0.66-0.79)	< 0.001
Osteopenia/osteoporosis	73 (65%)	30 (52%)	43 (78%)	0.010
Osteoporosis	19 (17%)	6 (11%)	13 (24%)	0.080

The statistics presented are the median and 25th-75th interquartile ranges.

Abbreviations: BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyltransferase; BAP, bone ALP; NTx, N-telopeptides of type I collagen; ASMI, appendicular skeletal muscle index; BMD, bone mineral density.

Table 2. Comparison of the clinical characteristics of patients with and those without cirrhosis.

Variables	Non-cirrhosis	Cirrhosis	P
N	72	40	
Age, years	65 (59-73)	69 (62-76)	0.061
Sex, male	34 (47%)	23 (58%)	0.32
BMI	22.9 (21.1-26.3)	25.4 (21.6-28.9)	0.11
Diabetes mellitus	14 (19%)	11 (28%)	0.35
Chronic kidney disease	12 (16%)	10 (25%)	0.33
Handgrip strength, kg	26 (21-32)	25 (17-32)	0.34
ASMI, kg/m²	6.65 (5.89-7.63)	7.04 (6.37-7.90)	0.22
Sarcopenia	8 (11%)	6 (15%)	0.56
Total bilirubin, mg/dL	0.8 (0.7-1.1)	0.8 (0.6-1.3)	0.90
Prothrombin time-INR	0.96 (0.92-1.00)	1.02 (0.98-1.14)	< 0.001
Serum albumin, g/dL	4.2 (4.0-4.5)	3.8 (3.5-4.3)	< 0.001
Serum creatinine, mg/dL	0.75 (0.64-0.97)	0.82 (0.65-0.96)	0.54

BAP, µg/L	14.7 (12.2-19.2)	17.7 (13.4-21.7)	0.11
Urine NTx, nmol/BCE/mmol Cr	31.8 (22.3-42.4)	25.6 (18.4-37.5)	0.30
FIB-4 index	1.91 (1.49-2.77)	3.65 (2.64-6.39)	< 0.001
Fibroscan, kPa	5.9 (4.7-8.1)	10.4 (8.0-15.6)	< 0.001
BMD lumbar spine, g/cm²	1.10 (0.99-1.23)	1.06 (0.83-1.23)	0.16
BMD femur neck, g/cm²	0.78 (0.71-0.87)	0.79 (0.69-0.86)	0.45
Osteopenia/osteoporosis	44 (61%)	29 (73%)	0.30
Osteoporosis	8 (11%)	11 (28%)	0.036

The statistics presented are the median and 25th-75th interquartile ranges.

Abbreviations: BMI, body mass index; BAP, bone ALP; NTx, N-telopeptides of type I collagen; ASMI, appendicular skeletal muscle index; BMD, bone mineral density.

Table 3. Comparison of clinical characteristics in patients with normal BMD, osteopenia and osteoporosis.

Variables	Normal BMD	Osteopenia	Osteoporosis	P
N	39	54	19	
Age, years	64 (58-72)	66 (60-73)	74 (66-80)	0.002
Sex, male	27 (69%)	24 (44%)	6 (31%)	0.01
BMI	25.1 (21.3-29.8)	23.6 (21.6-27.2)	22.6 (20.5-23.9)	0.047
Diabetes mellitus	12 (30%)	7 (12%)	6 (31%)	0.061
Chronic kidney disease	9 (23%)	7 (12%)	6 (31%)	0.15
Handgrip strength, kg	31 (25-37)	25 (21-30)	17 (16-26)	< 0.001
ASMI, kg/m²	7.52 (6.58-8.09)	6.65 (5.94-7.58)	6.20 (5.41-6.59)	< 0.001
Sarcopenia	0 (0%)	6 (11%)	8 (42%)	< 0.001
Hepatitis C	7 (17%)	19 (35%)	8 (42%)	0.093
Hepatitis B	5 (12%)	7 (12%)	2 (10%)	1
Alcohol	7 (17%)	6 (11%)	2 (10%)	0.65
NAFLD	13 (33%)	10 (18%)	4 (21%)	0.24
Autoimmune liver disease	7 (17%)	12 (22%)	3 (15%)	0.85

Cirrhosis	11 (28%)	18 (33%)	11 (57%)	0.081
Total bilirubin, mg/dL	0.8 (0.7-1.2)	0.9 (0.7-1.1)	0.8 (0.6-1.0)	0.45
Prothrombin time-INR	0.98 (0.92-1.02)	0.98 (0.95-1.05)	0.99 (0.93-1.02)	0.37
Serum albumin, g/dL	4.2 (3.9-4.4)	4.1 (3.8-4.4)	4.1 (3.7-4.4)	0.73
Serum creatinine, mg/dL	0.90 (0.66-0.98)	0.73 (0.61-0.97)	0.77 (0.67-0.98)	0.22
BAP, μg/L	16.9 (12.0-19.8)	15.0 (12.7-20.6)	15.5 (11.4-17.6)	0.79
Urine NTx, nmol/BCE/mmol Cr	23.2 (18.3-37.0)	33.1 (22.9-44.0)	35.5 (25.2-44.1)	0.065
FIB-4 index	2.04 (1.56-3.08)	2.59 (1.64-3.85)	2.79 (1.90-3.31)	0.29
Fibroscan, kPa	6.8 (4.8-10.6)	8.2 (5.7-9.4)	5.8 (5.2-8.1)	0.35
BMD lumbar spine, g/cm²	1.23 (1.16-1.29)	1.06 (0.98-1.12)	0.79 (0.75-0.83)	< 0.001
BMD femur neck, g/cm²	0.90 (0.85-0.98)	0.75 (0.71-0.79)	0.60 (0.56-0.66)	< 0.001

The statistics presented are the median and 25th-75th interquartile ranges. The clinical data were compared between groups using the Kruskal-Wallis test.

Abbreviations: BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; BAP, bone ALP; NTx, N-telopeptides of type I collagen; ASMI, appendicular skeletal muscle index; BMD, bone mineral density.

Table 4. Comparison of the clinical characteristics of patients with and without sarcopenia.

	All patients			Male patients			Female patients		
Variables	Sarcopenia (N = 14)	Non-sarcopenia (N = 98)	P	Sarcopenia (N = 5)	Non-sarcopenia (N = 52)	P	Sarcopenia (N = 9)	Non-sarcopenia (N = 46)	P
Age, years	73(63-80)	66 (59-73)	0.050	64 (58-70)	62 (59-80)	0.45	76 (66-80)	68 (61-75)	0.096
BMI	21.0 (19.5-21.7)	24.7 (21.7-28.1)	< 0.001	20.7 (20.7-21.8)	24.8 (22.1-28.9)	0.015	21.2 (19.4-21.6)	24.2 (21.6-27.9)	0.011
Cirrhosis	6 (42%)	34 (34%)	0.56	2 (40%)	21 (40%)	1	4 (44%)	13 (28%)	0.43
BAP, μg/L	15.1 (12.5-16.5)	15.3 (12.2-20.0)	0.65	15.6 (13.2-16.4)	14.7 (11.9-19.6)	0.55	14.7 (12.3-19.5)	15.5 (12.3-20.3)	0.86
Urine NTx, nmol/BCE/mmol Cr	37.2 (29.1-43.3)	28.9 (19.8-41.7)	0.31	39.6 (34.3-43.3)	23.5 (18.1-36.1)	0.20	35.5 (27.9-42.0)	36.8 (24.9-49.1)	0.71
BMD lumbar spine, g/cm²	0.98 (0.80-1.05)	1.11 (0.98-1.24)	0.001	1.03 (0.99-1.06)	1.22 (1.09-1.28)	0.009	0.85 (0.78-0.98)	1.01 (0.90-1.13)	0.049

BMD femur neck, g/cm²	0.64 (0.58-0.69)	0.80 (0.73-0.88)	< 0.001	0.71 (0.62-0.78)	0.85 (0.79-0.96)	0.018	0.62 (0.57-0.68)	0.74 (0.70-0.81)	< 0.001
Osteopenia/Osteoporosis	14 (100%)	59 (60%)	0.002	5 (100%)	25 (48%)	0.053	9 (100%)	34 (73%)	0.18
Osteoporosis	8 (57%)	11 (11%)	< 0.001	2 (40%)	4 (7%)	0.080	6 (66%)	7 (15%)	0.003

The statistics presented are the median and 25th-75th interquartile ranges. Abbreviations: BMI, body mass index; INR, international normalized ratio; BAP, bone alkaline phosphatase; NTx, N-telopeptides of type I collagen; BMD, bone mineral density.

Table 5. Multivariate linear regression analysis for bone mineral density.

	Lumbar spine					Femur neck				
Variables	Coefficient	95% CI		SE	P	Coefficient	95% CI		SE	P
Intercept	0.946	0.566	1.327	0.191	< 0.001	0.906	0.677	1.136	0.115	< 0.001
Age, years	0.003	-0.0009	0.007	0.002	0.13	-0.001	-0.003	0.0008	0.001	0.21
Sex, female	-0.190	-0.271	-0.109	0.040	< 0.001	-0.125	-0.174	-0.076	0.024	< 0.001
BMI	0.008	-0.0007	0.017	0.004	0.073	0.004	-0.0009	0.009	0.002	0.10
Cirrhosis	-0.160	-0.248	-0.072	0.044	< 0.001	-0.066	-0.119	-0.012	0.026	0.015
Urine NTx, nmol/BCE/mmol Cr	-0.002	-0.005	-0.0004	0.001	0.018	-0.0008	-0.002	0.0005	0.0007	0.21
Sarcopenia	-0.149	-0.268	-0.030	0.059	0.014	-0.110	-0.182	-0.038	0.036	0.003

Abbreviations: CI, confidence interval; SE, standard error; BMI, body mass index; NTx, N-telopeptides of type I collagen.

Table 6. Univariate and multivariate logistic analyses for the factors associated with osteoporosis in chronic liver disease.

	Univariate		Multivariate	
Variables	OR (95% CI)	P	OR (95% CI)	P
Age, years	1.11 (1.04-1.18)	0.002	1.10 (0.99-1.21)	0.054
Sex, female	2.63 (0.92-7.52)	0.071	4.20 (0.88-20.1)	0.071
BMI	0.85 (0.74-0.98)	0.031	0.73 (0.56-0.95)	0.021
Cirrhosis	3.03 (1.10-8.34)	0.031	15.8 (2.64-95.1)	0.002
Urine NTx, nmol/BCE/mmol Cr	1.02 (0.99-1.05)	0.18	1.04 (0.99-1.08)	0.060
Sarcopenia	10.5 (3.08-36.1)	< 0.001	6.16 (1.10-34.6)	0.039

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index.

Figure 1

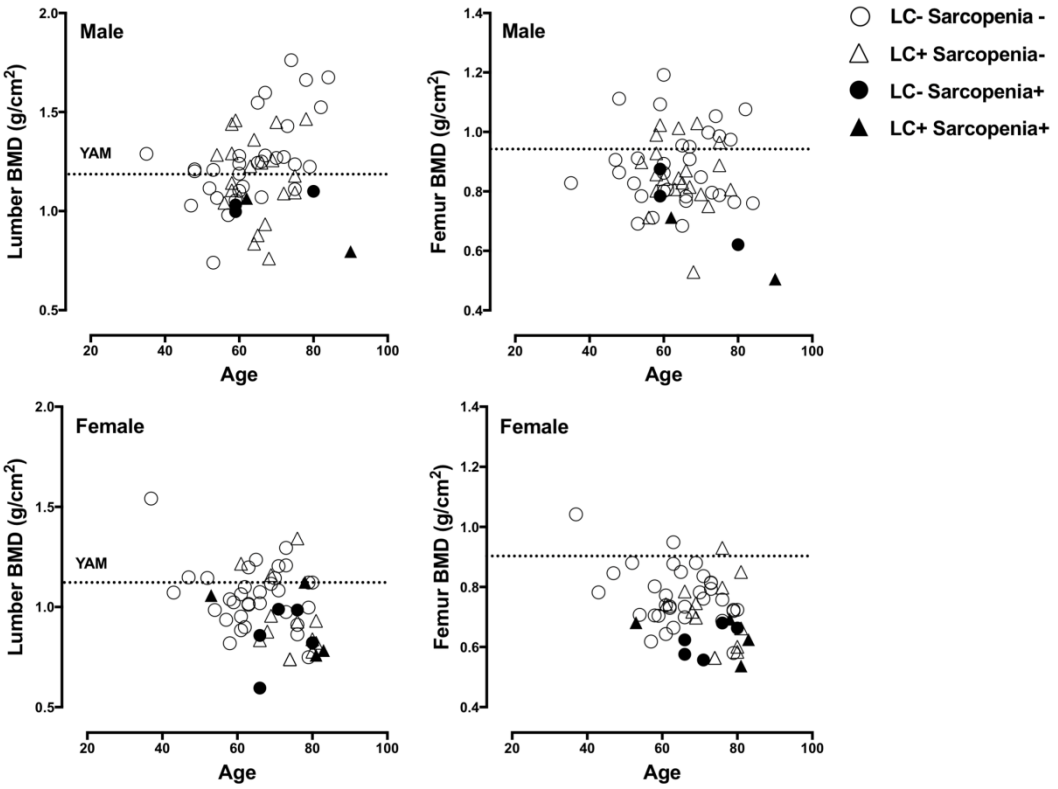

Figure 1. Relationship among age, bone mineral density (BMD), liver cirrhosis(LC) and sarcopenia. We classified patients into 4 groups; LC-/Sarcopenia- (○), LC+/Sarcopenia- (△), LC-/Sarcopenia+ (●) and LC+/Sarcopenia+ (▲). The BMD of patients with sarcopenia was less than the young adult mean (YAM) of BMD regardless of age. The YAM (dotted line) (lumber spine) was 1.19 g/cm^2 for males and 1.12 g/cm^2 for females. The YAM (femur neck) was 0.95 g/cm^2 for males and 0.90 g/cm^2 for females.

Figure 2

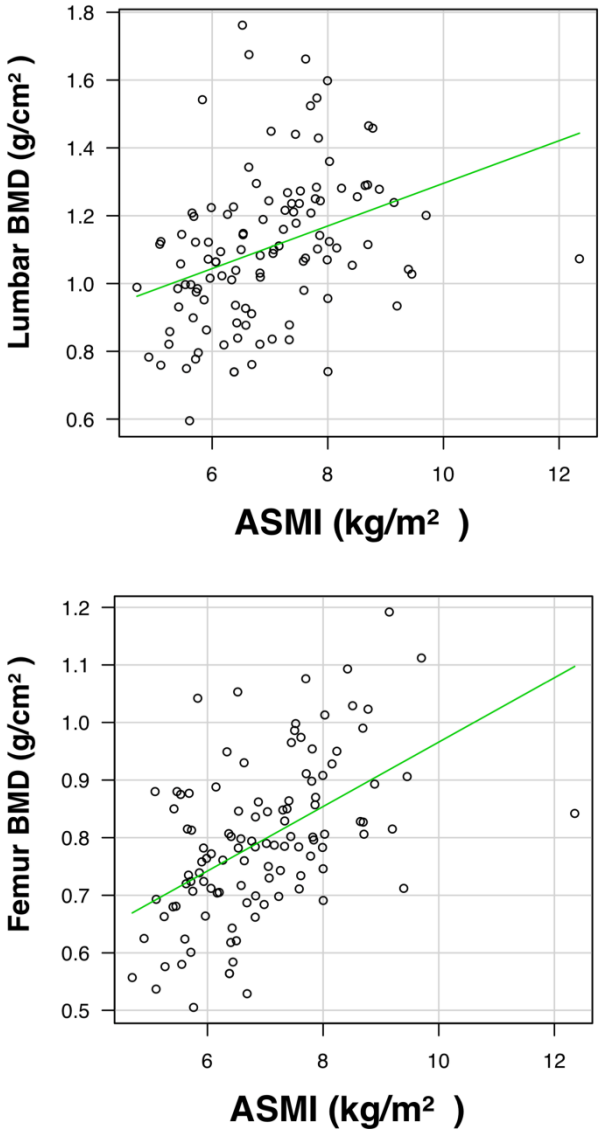

Figure 2. Correlations between appendicular skeletal muscle mass index (ASMI) and bone mineral density (BMD). The ASMI was significantly correlated with the BMD of the lumbar spine ($r = 0.44$, $P < 0.001$). The ASMI was significantly correlated with the BMD of the femur neck ($r = 0.52$, $P < 0.001$).

Figure 3

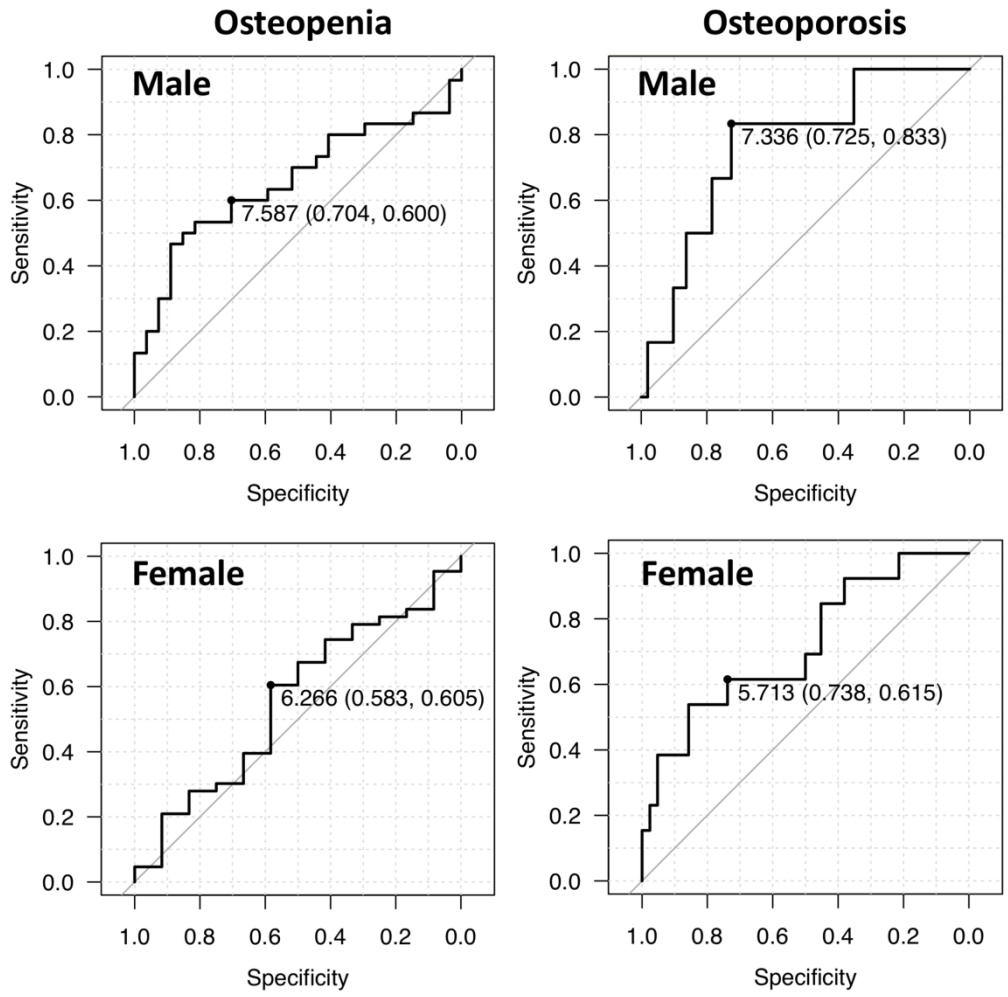

Figure 3. Area under the receiver operating characteristic (AUROC) of appendicular skeletal muscle mass index (ASMI) for predicting osteopenia and osteoporosis. The cut-off values of the ASMI (AUROC, specificity and sensitivity) for osteopenia and osteoporosis were 7.587 kg/m² (0.656, 0.600 and 0.704) and 7.336 kg/m² (0.768,

0.833 and 0.725), respectively, for male patients, and 6.266 kg/m² (0.554, 0.605 and 0.538) and 5.713 kg/m² (0.718, 0.615 and 0.738), respectively, for female patients.