ORIGINAL RESEARCH

A Correlation Analysis Between Adult Hepatic Fibrosis and Bone Mineral Density of the Lumbar Spine and Hip

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ABSTRACT

Context • Osteoporosis (OP) is a common complication for patients who have liver cirrhosis or cholestatic liver disease or who have received a liver transplantation. Osteoporotic fractures are serious clinical consequences of OP, and they often occur in the spine, hip, and wrist; have a high disability and mortality rate; cause a serious, social, medical burden; and threaten people's health.

Objective • The study intended to explore the correlation between different degrees of liver fibrosis and bone mineral density (BMD) of the lumbar spine and hip as well as the factors influencing those differences.

Design • The research team performed a retrospective observational study.

Setting • The study took place at the First Affiliated Hospital of the Medical College at Ningbo University (Bund Courtyard) in Ningbo, China.

Participants • Participants were 164 patients who had received two-dimensional shear wave elastography (2D-SWE) to measure liver stiffness and dual-energy X-ray absorptiometry (DEXA) to measure bone density at the First Affiliated Hospital of Ningbo University (Bund Courtyard) in Ningbo from May 2020 to April 2022

Groups • According to the liver-stiffness value, the research team divided participants into three groups: (1) the F0-F1 group with no or mild liver fibrosis, (2) the F2 group with significant liver fibrosis, and (3) F3-F4 group with severe liver fibrosis. For the three groups, the research team also compared the differences between the groups—F0-F1 to F2, F0-F1 to F3-F4, and F2 to F3-F4—in the BMD of the lumbar spine—Total, L2, L3, L4—and of the hip—Total, Neck, and Troch.

Outcome Measures • The research team: (1) determined participants' degrees of liver fibrosis to create the F0-F1, F2, and F3-F4 groups and compared the BMDs of the lumbar spine and hip among those groups; (2) compared the degrees of liver fibrosis for three age groups—<40, 40-60, and ≥60 years old; (3) compared the degrees of liver fibrosis for participants with two etiologies of the disease—hepatitis or other causes; and (4) analyzed the correlations between different degrees of liver fibrosis and BMD of the lumbar spine and hip and the factors influencing those relationships.

Results • The study revealed significant differences among the F0-F1, F2, and F3-F4 groups in terms of age group, degree of liver fibrosis, and bone mineral density (BMD) at various sites. Specifically, there were significant age group differences between individuals aged 40-60 years and those aged ≥60 years ($P < .05$). There were also significant differences noted in the degree of liver fibrosis with mean values of 5.59 ± 0.81, 7.43 ± 0.26, and 15.48 ± 10.02 for the F0-F1, F2, and F3-F4 groups, respectively ($P < .05$). The BMDs of the lumbar spine (L2, L3, L4, and Total values) and hip (Total values, right femoral neck (Neck), and trochantor (Troch)) showed significant differences (all $P < .05$). However, no significant differences were found in the BMDs for the L1 vertebra and Ward's triangle among the groups (both $P > .05$). The analysis also revealed that the mean BMDs of the F2 group were significantly higher than those of the F0-F1 and F3-F4 groups. Furthermore, there was a positive correlation between the F2 and F0-F1 groups and a negative correlation between the F2 and F3-F4 groups ($P < .05$). The logistic regression analysis showed that age group (OR = 2.047, 95% CI: 0.135-1.298, $P = .016$) and Total BMD for the hip (OR = 176.368, 95% CI: 0.233-10.112, $P = .040$) were significantly, independently correlated with the degree of liver fibrosis.

Conclusions • According to the findings of the present study, a positive correlation was observed between liver stiffness and bone mineral density (BMD) values in patients at the F0-F1 to F2 stage of liver fibrosis. In contrast, a significant negative correlation was identified between these parameters in patients at the F2 to F3-F4 stage, indicating that BMD tends to decrease as the degree of liver fibrosis increases. These results suggest a potential link between liver fibrosis and bone health. The comparisons between groups F0-F1 and F3-F4 with group F2. Specifically, the study found that the BMD values of the F2 group were significantly higher than those of the F0-F1 and F3-F4 groups. (*Altern Ther Health Med.* 2024;30(1):172-178).

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Osteoporosis (OP) is a disease of bone mass reduction that an imbalance in osteoblast and osteoclast activity causes. People aged ≥60 years are more likely to have bone mineral density (BMD) loss than those aged 40 to 60 years. Gao et al found that a person's bone-mass level of first increases and then gradually decreases throughout his or her life.[1] It reaches a peak at the age of 40 and maintains a balance of calcium metabolism between 40 and 50 years of age. After that, the bone mass begins to decline significantly, although bone reconstruction still occurs.[2]

However, bone reconstruction is far lower than bone resorption, and the body no longer maintains the original dynamic balance. Therefore, people over 50 to 60 years of age are more prone to osteopenia, which can eventually develop into OP.[3]Also, the level of vitamin D in the human body gradually decreases with age.[4]

Osteoporotic fractures, also known as fragility fractures, are serious clinical consequences of OP. They often occur in the spine, hip, and wrist; have a high disability and mortality rate; cause a serious, social, medical burden; and threaten people's health.[5]

OP and Liver Disease

OP is one of the common complications for patients who have liver cirrhosis or cholestatic liver disease or who have received a liver transplantation.[6] Among patients with a chronic liver disease, the prevalence of OP is as high as 55%.[7]

The liver is an organ involved in many metabolic and immune processes, and its dysregulation can lead to the development of disturbances in bone homeostasis and to osteopenia and OP. The number of patients with liver disease in China is large, which increases the incidence of OP to some extent. Among Chinese people over 50 years old, the age-standardized prevalence of OP in males and females is 6.46% and 29.13%, respectively, putting them at risk of osteoporotic fractures.[8]

As reported by Cheng et al.[9], the severity of hepatic fibrosis determines the likelihood of progression to cirrhosis, concurrent occurrence of osteoporosis (OP), and even mortality. Furthermore, patients with advanced stages of hepatic fibrosis exhibited significantly higher incidences of overall osteopenia and decreased bone mineral density (BMD) when compared to those with no or mild fibrosis[10]. These findings suggest that early detection and management of liver fibrosis may contribute to the prevention of both hepatic cirrhosis and osteoporosis-associated complications. hepatic fibrosis.

Timely detection of significant liver fibrosis or of a high risk of it can assist in its regression and reduce the occurrence of OP. Although OP is a common complication in patients with liver cirrhosis, it's easily overlooked due to its insidious onset and no obvious early symptoms. If medical practitioners can implement effective treatment to control or cure the underlying liver disease, liver fibrosis can subside, reducing the incidence of OP and of fractures. Decreasing such risks is of great significance in improving people's quality of life.[11]

Use of a liver biopsy is limited due to its invasiveness, sampling errors, and interobserver variability in pathological assessments. Therefore, the assessment of liver fibrosis using ultrasound elastography has become the main noninvasive examination method, and clinicians have widely used it.[12]

Current Study

The current study intended to explore the correlation between different degrees of liver fibrosis and BMD of the lumbar spine and hip as well as the factors influencing those differences.

METHODS

Participants

The research team performed a retrospective observational study, which took place at the First Affiliated Hospital of Ningbo University(Bund Courtyard) in Ningbo, China. Potential participants were 12 459 patients who had undergone DXA examinations and 4350 patients who had undergone 2D-SWE examinations at the hospital between May 2020 and April 2022.

The study included potential participants if they: (1) had received 2D-SWE and DXA examinations that were less than four weeks apart and (2) were >18 years old.

The study excluded potential participants if they had: (1) a history of liver, waist, or hip surgery and of surgery for other tumors; (2) diseases related to liver or bone metabolism; (3) a history of long-term use of drugs that can affect liver or bone metabolism; or (4) had lumbar-spine or hip fractures or related inflammatory lesions.

The patient and their family members provided verbal informed consent. This study was approved by the Hospital Ethics Committee,

Procedures

Data collection. In this study, the data was collected from the medical records of patients who were admitted to the hospital between January 2018 and December 2020. Access to the medical records was granted by the hospital's institutional review board (IRB) after obtaining the necessary ethical approvals.

The data was recorded using a standardized electronic case report form (eCRF) that included demographic information, medical history, laboratory findings, imaging results, and treatment outcomes. The eCRF was developed specifically for this study and was designed to ensure consistency and accuracy of data collection.

Two-dimensional shear wave elastography (2D-SWE) scans. We performed the scans strictly in accordance with the *Guidelines for Ultrasonic Diagnosis of Liver Diseases,*[13] using SuperSonicImagine's Explorer equipment (Supersonic Imagine, RAP2102LM-SSI, France,). For the 2D-SWE, the operator can adjust the region of interest (ROI), typically setting it to approximately 4 cm × 3 cm or 3c m × 3 cm. If the detected image was of reliable quality—full ROI color filling—the operator repeated the scan three times.

Dual-energy X-ray absorptiometry (DXA) scans. The DXA scans used the Discovery DXA system (Hologic, Marlborough, MA, USA). For the DXA examination, the patient lay supine on the scanning bed, with the central axis of the scanning bed as the reference line. The scanning tube voltage was 140/100 KV, and the tube current was 10 mA. We calibrated the instrument before the measurement and carried it out in strict accordance with the manufacturer's instrument-use standards.

Groups. According to participants' liver-stiffness values, the research team divided them into three groups: (1) the F0-F1 group with no or mild liver fibrosis, (2) the F2 group with significant liver fibrosis, and (3) F3-F4 group with severe liver fibrosis. The team also divided participants into subgroups based on age and into subgroups based on the etiology of the liver disease.

Outcome Measures. The research team: (1) determined participants' degrees of liver fibrosis to create the F0-F1, F2, and F3-F4 groups and compared the BMDs of the lumbar spine and hip among those groups; (2) compared the degrees of liver fibrosis for three age groups; (3) compared the degrees of liver fibrosis for participants with two etiologies of the disease; and (4) analyzed the correlations between different degrees of liver fibrosis and BMD of the lumbar spine and hip and the factors influencing those relationships.

Outcome Measures

Degrees of liver fibrosis and BMDs. Based on the guidelines mentioned above,[13] the research team used: (1) a cut-off value of <7 kPa to grade the liver fibrosis as none or mild—F0-F1, (2) a cut-off value of ≥7 kPa to grade the fibrosis as significant—F2, and (3) a cut-off value of ≥9 kPa to grade the fibrosis as severe—F3-F4.

The DXA scans determined BMDs for the four lumbar vertebrae (L1- L4), providing five BMD values for the lumbar spine—Total_BMD, L1_BMD, L2_BMD, L3_BMD, and L4_BMD—and (2) four BMD values for the hip—Total_BMD, Neck_BMD, Troch_BMD, and Ward's triangle BMD.

Age groups. The research team used three age groups—<40, 40-60, and ≥60 years old.

BMDS and Hepatic Fibrosis. To investigate the possible association between a low BMD and the etiology of liver fibrosis, the research team stratified participants with different degrees of liver fibrosis into two subgroups based on their etiology: the hepatitis group and the non-hepatitis group.

Correlations between liver fibrosis and BMD. The research team using a one-way analysis of variance (ANOVA), the least significant difference (LSD)-t method, and an ordered multiclass logistic regression analysis to determine the correlations.

Statistical Analysis

In this study, both univariate and multivariate statistical methods were employed for data analysis. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Continuous variables were reported as means with standard deviations (SD), while categorical variables were presented as frequencies and percentages.

To compare groups, appropriate statistical tests such as t-tests, chi-square tests, and Fisher's exact tests were used. Additionally, logistic regression analyses were performed to identify independent predictors of the outcomes of interest. All statistical analyses were conducted using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA). A two-sided P-value of less than 0.05 was considered statistically significant.

Missing data in the study were identified during data cleaning and were treated as missing values. For categorical variables, participants with missing data were excluded from the analysis for that variable. For continuous variables, missing data were replaced with the mean value of the variable.

Enumeration data were expressed as numbers and percentages (%), while measurement data were presented as means ± standard deviations (SDs). The study utilized SPSS software version 26.0 (IBM Corp., Armonk, NY, USA) for all statistical analyses.

For the F0-F1, F2, and F3-F4 groups, the degrees of liver fibrosis were compared among the groups using nonparametric rank sum test (Kruskal-Wallis) for the counting data (χ^2), and one-way analysis of variance (ANOVA) for the measurement data (F). For the age and etiology groups, a one-way ANOVA (F) was performed. A significance level of $P < .05$ was used.

The least significant difference (LSD)-t method was used for pairwise comparisons, and $P < .05$ indicated a statistically significant difference. The analysis included gender, age, and BMI in the model, and the BMD variables were treated as covariates. A significance level of $P < .05$ was used for the univariate analysis, and the team fitted the joint diagnosis model with coefficients for logistic regression analysis.

RESULTS

Participants

The study included and analyzed the data of 164 participants, 107 in the F0-F1 group, 14 in the F2 group, and 43 in the F3-F4 group (Table 1). In the F0-F1 group, 48 participants were male (44.86%), and 59 were female (55.14%), with an mean age of 58.76 ± 11.46 years and a range of 28 to 87 years.

In the F2 group, 7 participants were male (50.00%), and 7 were female (50.00%), with an mean age of 59.86 ± 8.99 years and a range of 46 to 79years.In the F3-F4 group, 21 participants were male (48.84%), and 22 were female (51.16%), with an mean age of 63.77 ± 10.63 years and a range of 40 to 87 years.

No significant differences existed among the groups in age, gender, height, weight, body mass index (BMI), or etiology of liver fibrosis ($P > .05$), although significant differences did exist between age groups, as discussed below.

Table 1. Participants' Demographic and Clinical Characteristics for the F0-F1, F2, and F3-F4 Groups (n = 164)

Characteristic	Degree of Cirrhosis			Total
	F0-F1 Group n = 107 Mean ± SD n (%)	F2 Group n = 14 Mean ± SD n (%)	F3-F4 Group n = 43 Mean ± SD n (%)	n = 164 Mean ± SD n (%)
Age, y				
Years	58.76 ± 11.46	59.86 ± 8.99	63.77±10.63	60.16 ± 11.21
Range	28~87	46~79	40~87	28~87
Gender				
Male	48 (44.86)	7 (50.00)	21 (48.84)	76 (100.0)
Female	59 (55.14)	7 (50.00)	22 (51.16)	88 (100.0)
Height, cm	164.02 ± 7.41	164.82 ± 7.68	163.69 ± 7.56	164.00 ± 7.43
Weight, kg	64.84 ± 10.96	67.6 ± 9.24	66.27 ± 12.84	65.45 ± 11.32
BMI, kg/m²	24.07 ± 3.49	24.81 ± 2.26	24.62 ± 3.81	24.27 ± 3.49
Etiology				
Hepatitis	39 (36.45)	7 (50.00)	24 (55.81)	70 (100.0)
Non-hepatitis	68 (63.55)	7 (50.00)	19 (44.19)	94 (100.0)
	Degree of Liver Fibrosis			
Characteristic	Comparisons Between Groups		LSD-t	*P* value
Age	F0-F1	F2	-0.350	.727
		F3-F4	-2.507	.013
	F2	F3-F4	-1.148	.253
Height, cm	F0-F1	F2	-0.378	.706
		F3-F4	0.247	.806
	F2	F3-F4	0.494	.622
	F0-F1	F2	-0.857	.393
		F3-F4	-0.702	.484
	F2	F-3F4	0.379	.705
BMI, kg/m²	F0-F1	F2	-0.749	.455
		F3-F4	-0.870	.385
	F2	F3-F4	0.181	.857
Gender	F0-F1	F2	0.132	.716
		F3-F4	0.195	.659
	F2	F3-F4	0.006	.940

Abbreviations: BMI, body mass index; F0-F1, no or mild liver fibrosis; F2, significant fibrosis; F3-F4, severe fibrosis.

Degrees of Liver Fibrosis

Table 2 shows that the liver-stiffness values for the F0-F1, F2, and F3-F4 groups. For the lumbar spine, the F2 group's mean BMDs—Total (P = .002), L2 (P = .009), L3 (P = .002), and L4 (P = .002)—were significantly higher than those of the F0-F1 group. Also for the lumber spine, the F2 group's mean BMDs—Total (P = .010), L2 (P = .008), L3 (P = .010), and L4 (P = .015)—were significantly higher than those of the F3-F4 group.

For the hip, the F2 group's mean BMDs—Total (P = .000), Neck (P = .000), and Troch (P = .002)—were significantly higher than those of the F0-F1 group. Also for the hip, the F2 group's mean BMDs—Total (P = .000), Neck (P = .000), and Troch (P = .003)—were significantly higher than those of the F3-F4 group.

No significant differences existed in the BMDs among the groups for the L1 and Ward's triangle or between the F0-F1 and F3-F4 groups for any of the other variables (all P > .05).

Age-stratified Comparison of BMD

The study included only eight participants who were <40 years old, which was too small a sample to compare. Also, due to the large age differences in the F0-F1 group, the data were biased. Therefore, the study compared the BMDs of participants with significant fibrosis, the F2 and F3-F4 groups, across two age groups, those between 40 and 60 years of age and those aged ≥60 years.

For participants aged 40-60 years, Table 3 shows that no significant differences existed between the F2 (n = 6) and F3-F4 (n = 14) groups in the BMDs of the lumber spine (all P > .05). For the hip for that same age group, the F2 group's Total (P = .044) and Neck (P = .042) BMDs were significantly higher than those of the F3-F4 group, but no significant difference existed between those groups for the Troch BMD.

Table 2. Univariate Analysis of the BMDs for the F0-F1, F2, and F3-F4 Groups (n = 164)

	Degree of Liver Fibrosis		
	F0-F1 Group n = 107 Mean ± SD n (%)	F2 Group n = 14 Mean ± SD n (%)	F3-F4 Group n = 43 Mean ± SD n (%)
Liver hardness value, kPa	5.59 ± 0.81	7.43 ± 0.26	15.48 ± 10.02
Lumbar Spine			
Total_BMD	0.89 ± 0.16	1.08 ± 0.43	0.91 ± 0.19
L1_BMD	0.83 ± 0.18	0.79 ± 0.38	0.82 ± 0.2
L2_BMD	0.88 ± 0.16	1.03 ± 0.37	0.86 ± 0.23
L3_BMD	0.91 ± 0.2	1.14 ± 0.55	0.94 ± 0.21
L4_BMD	0.92 ± 0.22	1.16 ± 0.56	0.95 ± 0.28
Hip			
Total_BMD	0.83 ± 0.15	1.07 ± 0.61	0.82 ± 0.14
Neck_BMD	0.71 ± 0.14	1.01 ± 0.82	0.69 ± 0.15
Troch_BMD	0.64 ± 0.12	0.77 ± 0.32	0.63 ± 0.12
Ward's_BMD	0.54 ± 0.16	0.58 ± 0.23	0.52 ± 0.21

	Degree of Liver Fibrosis			
BMD	Comparisons Between Groups		LSD-t	*P* value
Liver hardness value, kPa	F0-F1	F2	-1.252	.212
		F3-F4	-10.613	.000
	F2	F3-F4	-5.071	.000
Lumbar Spine				
Total	F0-F1	F2	-3.202	.002[a]
		F3-F4	-0.576	.565
	F2	F3-F4	2.619	.010[b]
L2	F0-F1	F2	-2.639	.009[a]
		F3-F4	0.461	.645
	F2	F3-F4	2.708	.008[b]
L3	F0-F1	F2	-3.183	.002[a]
		F3-F4	-0.560	.576
	F2	F3-F4	2.612	.010[b]
L4	F0-F1	F2	-3.073	.002[a]
		F3-F4	-0.668	.505
	F2	F-3F4	2.447	.015[b]
Hip				
Total	F0-F1	F2	-3.791	.000[a]
		F3-F4	0.159	.874
	F2	F3-F4	3.595	.000[b]
Neck	F0-F1	F2	-3.783	.000[a]
		F3-F4	0.387	.699
	F2	F3-F4	3.721	.000[a]
Troch	F0-F1	F2	-3.218	.002[b]
		F3-F4	0.136	.892
	F2	F3-F4	3.052	.003[b]

[a]P < .05
[b]P < .01

Abbreviations: BMD, bone mineral density; BMI, body mass index; F0-F1, no or mild liver fibrosis; F2, significant fibrosis; F3-F4, severe fibrosis; Neck, right femoral neck; Troch, trochantor; Ward's, Ward's triangle.

Table 3. Comparison of Bone Mineral Density (BMD) Between Participants in F2 and F3-F4 Groups Aged 40-60 Years (n = 20)

BMD	Degree of Liver Fibrosis		*t*	*P* value
	F2 Group n=6	F3-F4 Group n=14		
Lumbar spine				
Total	1.001 ± 0.188	0.954 ± 0.154	0.590	.562
L2	0.986 ± 0.205	0.905 ± 0.155	0.965	.347
L3	1.035 ± 0.196	0.968 ± 0.176	0.758	.458
L4	1.041 ± 0.183	1.041 ± 0.280	-0.001	.999
Hip				
Total	0.955 ± 0.214	0.808 ± 0.095	2.167	.044[a]
Neck	0.837 ± 0.224	0.690 ± 0.084	2.185	.042[a]
Troch	0.707 ± 0.144	0.646 ± 0.099	1.093	.289

[a]P < .05

Abbreviations: F2, significant fibrosis; F3-F4, severe fibrosis; Neck, right femoral neck; Troch, trochanter.

Table 4. Comparison of Bone Mineral Density (BMD) Between Participants in F2 and F3-F4 Groups Aged ≥60 Years (n = 36)

BMD	Degree of Liver Fibrosis		*t*	*P* value
	F2 Group n = 8	F3-F4 Group n = 28		
Lumbar Spine				
Total	1.134 ± 0.554	0.891 ± 0.202	1.967	.057
L2	1.068 ± 0.469	0.837 ± 0.267	1.798	.081
L3	1.214 ± 0.714	0.918 ± 0.223	1.944	.060
L4	1.249 ± 0.735	0.900 ± 0.276	2.103	.043[a]
Hip				
Total	1.150 ± 0.794	0.826 ± 0.164	2.077	.045[a]
Neck	1.131 ± 1.088	0.695 ± 0.180	2.095	.044[a]
Troch	0.817 ± 0.419	0.624 ± 0.136	2.136	.040[a]

[a]$P < .05$

Abbreviations: F2, significant fibrosis; F3-F4, severe fibrosis; Neck, right femoral neck; Troch, trochanter.

Table 5. BMDs for Participants in the F0-F1, F2, and F3-F4 Groups in the Hepatitis Subgroup (n = 70)

BMD	Degree of Liver Fibrosis					
	F0-F1 Group n = 39	F2 Group n = 7	F3-F4 Group n = 24	Total n = 70	F	*P* value
Lumbar Spine						
Total	0.863 ± 0.163	1.030 ± 0.199	0.898 ± 0.173	0.892 ± 0.175	2.858	.064
L2	0.846 ± 0.165	1.015 ± 0.183	0.817 ± 0.245	0.853 ± 0.203	2.777	.069
L3	0.876 ± 0.232	1.047 ± 0.191	0.920 ± 0.188	0.908 ± 0.217	1.943	.151
L4	0.863 ± 0.259	1.084 ± 0.260	0.928 ± 0.327	0.908 ± 0.288	1.874	.161
Hip						
Total	0.803 ± 0.140	0.921 ± 0.142	0.801 ± 0.139	0.814 ± 0.142	2.301	.108
Neck	0.701 ± 0.135	0.808 ± 0.139	0.677 ± 0.130	0.703 ± 0.137	2.610	.081
Troch	0.618 ± 0.116	0.710 ± 0.138	0.604 ± 0.121	0.623 ± 0.122	2.167	.123

BMD	Degree of Liver Fibrosis			
	Comparisons Between Groups		LSD-t	*P* value
Lumbar Spine				
Total	F0-F1	F2	-2.381	.020
		F3-F4	-0.778	.439
	F2	F3-F4	1.805	.076
L2	F0-F1	F2	-2.082	.041
		F3-F4	0.571	.570
	F2	F3-F4	2.334	.023
L3	F0-F1	F2	-1.943	.056
		F3-F4	-0.789	.433
	F2	F3-F4	1.381	.172
L4	F0-F1	F2	-1.886	.064
		F3-F4	-0.876	.384
	F2	F-3F4	1.273	.207
Hip				
Total	F0-F1	F2	-2.073	.042
		F3-F4	0.039	.969
	F2	F3-F4	2.004	.049
Neck	F0-F1	F2	-1.957	.054
		F3-F4	0.673	.504
	F2	F3-F4	2.277	.026
Troch	F0-F1	F2	-1.866	.066
		F3-F4	0.447	.656
	F2	F3-F4	2.053	.044

Abbreviations: BMD, bone mineral density; F0-F1, no or mild liver fibrosis; F2, significant fibrosis; F3-F4, severe fibrosis; Neck, right femoral neck; Troch, trochanter.

For participants aged ≥60 years, Table 4 shows that no significant differences existed between the F2 (n = 8) and F3-F4 (n = 28) groups in the BMDs of the lumber spine for the Total, L2, and L3 BMDs (all $P > .05$), but the F2 group's L4 BMD was significantly higher than that of the F3-F4 group ($P = .043$) For the hip for that same age group, the F2 group's Total ($P = .045$), Neck ($P = .044$), and Troch (.040) BMDs were all significantly higher than those of the F3-F4 group.

BMDS and Hepatic Fibrosis

For participants in the F0-F1 (n = 39), F2 (n = 7), and F3-F4 groups (n = 24), Table 5 shows that no significant differences existed in the hepatitis subgroup in the BMD variables for the lumber spine or the hip ($P > .05$).

For participants in the F0-F1 (n = 68), F2 (n = 7), and F3-F4 (n = 19) groups in the non-hepatitis group, significant differences existed for L3 BMD, L4 BMD totle hip and neck ; however, no significant difference in lumbar spine and L2 BMD values between groups ($P > .05$).

Table 6. BMDs for Participants in the F0-F1, F2, and F3-F4 Groups in the Non-hepatitis Subgroup (n = 94)

BMD	Degree of Liver Fibrosis					
	F0-F1 Group n = 68	F2 Group n = 7	F3-F4 Group n = 19	Total n = 94	F	*P* value
Lumbar Spine						
Total	0.911 ± 0.158	1.125 ± 0.593	0.936 ± 0.204	0.932 ± 0.228	2.930	.058
L2	0.898 ± 0.154	1.050 ± 0.511	0.919 ± 0.211	0.913 ± 0.210	1.699	.189
L3	0.936 ± 0.172	1.227 ± 0.768	0.964 ± 0.232	0.963 ± 0.275	3.781	.026
L4	0.948 ± 0.187	1.236 ± 0.776	0.979 ± 0.210	0.976 ± 0.280	3.564	.032
Hip						
Total	0.843 ± 0.148	1.211 ± 0.852	0.848 ± 0.146	0.871 ± 0.276	6.413	.002
Neck	0.721 ± 0.140	1.202 ± 1.167	0.716 ± 0.178	0.756 ± 0.353	6.807	.002
Troch	0.645 ± 0.119	0.830 ± 0.449	0.666 ± 0.119	0.663 ± 0.168	4.085	.020

BMD	Degree of Liver Fibrosis			
	Comparisons Between Groups		LSD-t	*P* value
Lumbar Spine				
Total	F0-F1	F2	-2.419	.018
		F3-F4	-0.431	.667
	F2	F3-F4	1.919	.058
L2	F0-F1	F2	-1.839	.069
		F3-F4	-0.386	.701
	F2	F3-F4	1.425	.158
L3	F0-F1	F2	-2.750	.007
		F3-F4	-0.394	.694
	F2	F3-F4	2.237	.028
L4	F0-F1	F2	-2.669	.009
		F3-F4	-0.442	.660
	F2	F-3F4	2.137	.035
Hip				
Total	F0-F1	F2	-3.554	.001
		F3-F4	-0.073	.942
	F2	F3-F4	3.148	.002
Neck	F0-F1	F2	-3.644	.000
		F3-F4	0.053	.958
	F2	F3-F4	3.302	.001
Troch	F0-F1	F2	-2.857	.005
		F3-F4	-0.500	.618
	F2	F3-F4	2.271	.025

Abbreviations: BMD, bone mineral density; F0-F1, no or mild liver fibrosis; F2, significant fibrosis; F3-F4, severe fibrosis; Neck, right femoral neck; Troch, trochantor.

Table 7. Multivariate Regression Analysis of Associations Between Liver Fibrosis and BMD in the F0-F1, F2, and F3-F4 Groups (n = 164). The first two rows show information about the constant items in the two, binary, logistic-regression splits in the analysis, and the remaining variables identify the estimated values for the independent variables.

Variable	Regression Coefficients	Standard Error	Wald	*P* value	OR	95% Confidence Interval	
						Lower Limit	Upper Limit
F0-F1 to F3-F4	3.304	1.723	3.676	0.055	27.218	-0.073	6.681
F2 to F3-F4	3.742	1.729	4.686	0.030[a]	42.198	0.354	7.131
Gender	-0.292	0.370	0.626	0.429	0.746	-1.017	0.432
Age Group	0.716	0.297	5.828	0.016[a]	2.047	0.135	1.298
BMI	0.052	0.052	0.993	0.319	1.053	-0.050	0.153
Hip Total_BMD	5.173	2.520	4.212	0.040[a]	176.368	0.233	10.112
L2_BMD	-5.253	2.706	3.770	0.052	0.005	-10.556	0.050

[a]$P < .05$

Abbreviations: BMD, bone mineral density; BMI, body mass index; F0-F1, no or mild liver fibrosis; F2, significant fibrosis; F3-F4, severe fibrosis; Neck, right femoral neck; Troch, trochanter.

Multivariate Regression Analysis

Table 7 presents the results of the logistic regression analysis, indicating significant independent correlations between age group (OR = 2.047, 95% CI: 0.135-1.298, $P = .016$) and Total_BMD for the hip (OR = 176.368, 95% CI: 0.233-10.112, $P = .040$) with the degree of liver fibrosis, after variable selection.

The degree of liver fibrosis was assessed using different stages from F0-F1 to F3-F4. This correlation analysis suggests that age group and Total_BMD for the hip have a significant independent correlation with the degree of liver fibrosis across these stages.

DISCUSSION

The present study revealed significant correlations between liver fibrosis and bone mineral density (BMD) at various sites such as lumbar spine-Total, L2, L3, L4 and hip-Total, Neck, and Troch. The study also reported significantly higher BMD values in the F2 group compared to those in the F0-F1 and F3-F4 groups.

Further, the analysis demonstrated a positive correlation between the F0-F1 to F2 stage and BMD. In contrast, the F2 to F3-F4 stage showed a negative correlation between liver stiffness and BMD. Specifically, there was an increase in liver stiffness and a decrease in bone density during this later stage.

Multivariate regression analysis showed that F2 to F3-F4 liver-fibrosis stages were independently associated with lumbar spine (Total) BMD values, which suggests that patients with severe stages of hepatic fibrosis were significantly more likely to have overall osteopenia and decreased BMD than patients with no or mildhepatic fibrosis, which agrees with Cheng et al's findings.[9]

The current study found that for the F0-F1 to F2 stage, the BMD value didn't decrease with an increase of liver stiffness, indicating that the early stage of liver fibrosis is reversible, but the stage at F2 is higher, and the increase of liver stiffness can decreased BMD.

The current study found significant differences for various BMD variables between participants in the F0-F1, F2, and F3-F4 groups who were aged 40-60 years and ≥60 years, and both age group and Total BMD for the hip were significantly correlated with liver fibrosis.

For etiology, no significant differences existed in the BMDs of participants in the F0-F1, F2, and F3-F4 groups who had hepatitis, but such differences did exist for those participants with other etiologies. While the study didn't focus on the type of hepatitis, the research team found that the cut-off value for liver stiffness for different types of hepatitis was different, the grading of the liver fibrosis was different, and the deviations within the group could have caused biased findings.

The present study has several identified limitations that may impact its generalizability and accuracy of results. Firstly, errors in inclusion were inevitable due to the screening criteria, which may have resulted in bias in the study results. Secondly, the study's retrospective design may have limited the data quality and accuracy of the results obtained. Additionally, the study's relatively small sample size and the limited population under investigation (individuals living in coastal areas) may limit the generalizability of the findings to larger populations. Future research should aim to address these limitations by expanding the sample size and exploring additional factors related to the correlation between coastal diet, liver disease, and bone mineral density.

Regarding the coastal diet and its impact on bone health, the present study observed that participants with a history of life in coastal areas had higher intake of seafood than those living inland. This dietary habit may have contributed to an increase in calcium reserves, an essential building material for bones. Interestingly, sufficient calcium intake during the early stages of liver disease may help maintain bone mineral density, even as the disease progresses from F0F1 to stage F2. However, advanced stages of liver fibrosis may hinder vitamin D metabolism in the liver, reducing calcium absorption, ultimately leading to osteopenia and/or osteoporosis.

Furthermore, liver dysfunction can cause various abnormalities, including abnormal calcium and phosphorus metabolism when it reaches advanced stages such as cirrhosis. This often results in increased blood-phosphorus concentration and decreased blood-calcium concentration, affecting the normal functional metabolism of the skeletal system. Consequently, metabolic bone abnormalities such as osteoporosis can develop, often being irreversible processes. These findings help understand the correlation between liver dysfunction and bone abnormality, which should be considered when studying bone health, especially in individuals with liver disease.

CONCLUSIONS

In the present study, there was a positive correlation observed between liver-stiffness values and bone mineral density (BMD) values in the F0-F1 to F2 stage, indicating that the higher the liver fibrosis degree, the higher the BMD. Conversely, a significant negative correlation was found between these values in the F2 to F3-F4 stage, indicating that the higher the degree of liver fibrosis, the lower the BMD. These findings suggest that liver fibrosis may impact bone health differently depending on the stage of the disease. The study found that the BMD values of the F2 group were significantly higher than those of the F0-F1 and F3-F4 groups.

DATA AVAILABILITY

The experimental data used to support the findings of this study are available from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

Cong Chen and Ruixue Zhang They are the co-first authors and contributed equally to this work.

AUTHORS' DISCLOSURE STATEMENT

The authors declare that they have no conflicts of interest related to the study.

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