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RESEARCH

Optimal body mass index for protecting middle-aged and elderly patients with fatty liver from future fractures

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Abstract

Objective: Previous studies have suggested that body mass index (BMI) should be considered when assessing the relationship between fatty liver (FL) and osteoporosis. The aim of this study was to investigate future fracture events in people with FL, focusing on the effect of BMI in both sexes.

Methods: This retrospective cohort study, spanning from 2011 to 2019, enrolled 941 people, including 441 women and 500 men, aged 50 years or older who underwent liver imaging (ultrasound, computed tomography, or magnetic resonance image) and dual-energy X-ray absorptiometry (for bone mineral density measurements). The study examined predictors of osteoporosis in both sexes and the effect of different ranges of BMI (18.5–24, 24–27, and ≥27 kg/m^2) on the risk of future fracture events in FL patients.

Results: The average follow-up period was 5.3 years for women and 4.2 years for men. Multivariate analysis identified age and BMI as independent risk factors of osteoporosis in both sexes. Each unit increase in BMI decreased the risk of osteoporosis by ≥10%. In both women and men with FL, a BMI of 24–27 kg/m^2 offered protection against future fractures, compared to those without FL and with a BMI of 18.5–24 kg/m^2.

Conclusion: The protective effect of a higher BMI against future fractures in middle-aged and elderly female and male patients with FL is not uniform and diminishes beyond certain BMI ranges.

Keywords: fatty liver; osteoporosis; fracture; body mass index; bone mineral density

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Introduction

Fatty liver (FL), a condition of increasing global prevalence, is estimated to affect up to 32% of adults worldwide by 2022 (1). FL is known for its systemic interactions with extrahepatic organs and its complexity beyond liver manifestations (2).

Previous studies have identified that FL may be associated with bone mineral density (BMD) and osteoporosis. However, these associations have been inconsistent. Some studies have demonstrated that FL negatively affects BMD and increases the risk of osteoporosis (3, 4, 5). Another study has reported no association between FL and BMD or osteoporosis in patients after adjusting for body mass index (BMI) (6). However, other studies have indicated that FL may be associated with reduced bone density loss or a lower risk of osteoporosis (7). These results suggest that BMI may mediate the protective effects of FL on the reduction of BMD loss or the risk of osteoporosis (7). Therefore, BMI should be considered when evaluating the association between FL and bone loss or osteoporosis. What is more, there is evidence that women with a low BMI are more likely to have osteopenia and develop osteoporosis (8). A high BMI may have a protective effect on femoral neck BMD. Both women and men with a high BMI have a lower risk of developing osteoporosis than those with a normal BMI (9). In addition to low BMI, advancing age is known to be an important risk factor for developing low BMD (10). Low BMD or osteoporosis leads to future fractures with a more severe clinical impact in the elderly. Having a higher BMI might be a strategy to prevent osteoporosis, as studies have observed a correlation between higher BMI and a decrease in osteoporosis-related fractures in both women and men (11).

Postmenopausal women have a higher prevalence of osteoporosis and a higher incidence of fractures than older men (12). The decline in estrogen during menopause accelerates bone loss in women, whereas men experience a more gradual decline in bone density. Therefore, examining women and men separately when evaluating BMD loss, osteoporosis, and future fracture risk as outcomes may be more appropriate. This study aimed to investigate future fracture risk in middle-aged and elderly patients with and without FL according to sex, considering the role of BMI.

Materials and methods

Study participants

The population of this retrospective cohort longitudinal follow-up study was identified from patients who underwent imaging, including abdominal ultrasound, CT, and MRI, for the diagnosis of FL in a tertiary referral center between 2011 and 2019. All the patients were followed up until July 2023 (Fig. 1). The inclusion criteria were: abdominal imaging tests (including ultrasound, CT, and MRI) were performed and reported by a radiologist or gastroenterologist to determine the presence of FL; age of 50 years or more; underwent axial dual-energy X-ray absorptiometry (DXA) scan (13), including at least the lumbar spine or hip, for bone density measurement within 6 months before or after their abdominal imaging; and had at least 1 year of medical records in the hospital prior to study participation.

Patients with a history of organ transplantation, malignancy, viral hepatitis, liver cirrhosis, hepatic failure, immunologic or rheumatic disease, end-stage renal disease (as documented in the medical records using the ICD-9-CM 586 or ICD-10-CM N19 codes), or dialysis, osteomalacia, parathyroid disease, a documented history of steroid use for >3 months, or excessive alcohol consumption were excluded. According to Taiwan's Ministry of Health and Welfare, the standard for appropriate daily alcohol consumption is no more than two units of alcohol for adult males and one unit for females, with one unit equal to 10 g of pure alcohol (https://www.mohw.gov.tw/cp-6562-75242-1.html). The date of the DXA examination was designated as the date of enrollment. During the follow-up period, changes in BMD were compared in patients who underwent a second bone densitometry follow-up.

Baseline data collection

Baseline demographic data and medical histories were recorded through a chart review. These included sex, age, height, BMI, current smoking status, and current alcohol consumption. The use of an osteoporotic agent within 1 year prior to enrollment for all participants was documented. Hormone replacement therapy (HRT) in women was also reviewed. Treatment for osteoporosis included the following prescribed osteoporosis drugs: bisphosphonates, denosumab, and selective estrogen receptor modulators in antiresorptive drugs; recombinant human parathyroid hormone teriparatide; and romosozumab in anabolic drugs (14). In addition, abdominal (liver) imaging results, DXA reports (including BMD and *T*-score values of the lumbar spine or hip), and laboratory results of plasma biochemical parameters were collected. Definitions of hypertension and diabetes were based on entries in the hospital's outpatient or inpatient medical charts or ongoing prescription records. Osteoporosis was diagnosed according to the guidelines of the World Health Organization, which defines osteoporosis or osteopenia based on *T*-score results. A *T*-score of BMD ≤ −2.5 was defined as osteoporosis, and a *T*-score ranging between −1 and −2.5 was considered osteopenia. Osteoporosis was diagnosed if a patient had a *T*-score ≤ −2.5 at any part of the hip or lumbar (15).

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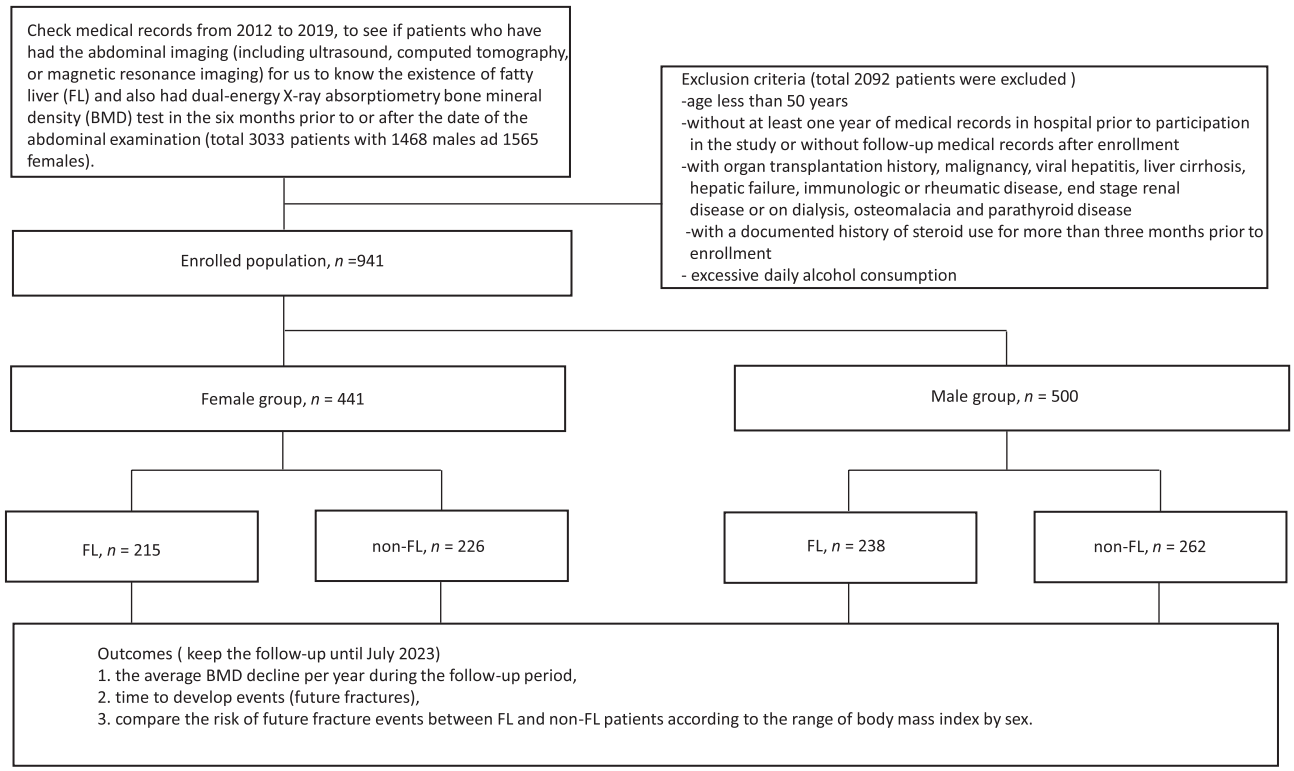

Figure 1

Study design and algorithm.

Outcome data collection

Study outcomes were future fracture events (new fractures occurring after the day of enrollment, but not within 1 month of enrollment) based on an investigation of these enrolled patients' medical records and corresponding imaging reports until a fracture occurred. Fractures occurring in a setting of low-level or low-energy trauma, defined as falling from standing height or less, are usually related to osteoporosis (16). Thus, fractures related to high-energy trauma, such as traffic accidents or falls from height, were excluded. Fracture-free survival (FFS) was calculated by follow-up until the patient last visited our hospital. The BMI (kg/m^2) was calculated using the following formula: weight in kilograms divided by height in meters squared.

A recent study has suggested that maintaining an appropriate BMI range can minimize the risk of osteoporosis, which reflects the risk of fracture (17). Accordingly, a subgroup analysis was conducted to examine the varying effects of BMI range on the risk of future fracture. The Taiwanese Health and Welfare Ministry's BMI criteria were used to categorize BMI. Underweight was defined as BMI ≤ 18.5 kg/m^2, normal as 18.5 ≤ BMI < 24 kg/m^2, overweight as 24 ≤ BMI < 27 kg/m^2, and obese as BMI ≥ 27 kg/m^2 (Ministry of Health and Welfare in Taiwan. Evidence-based guideline on adult obesity prevention and management. Available at https://www.hpa.gov.tw/Pages/EBook.aspx?nodeid=1788). In both sexes, non-FL patients with a BMI within the normal range were used as the reference group to compare the HRs.

Statistical analysis

For categorical data, baseline descriptive variables are expressed as percentages, and normally distributed continuous data are expressed as means ± S.D.. For comparisons between the two groups of patients, the Chi-square and Student's *t*-tests were used for categorical variables and numerical data, respectively. Predictors of osteoporosis were evaluated using univariate and multivariate logistic regressions. Odds ratios (ORs) and 95% CIs were determined. Kaplan–Meier survival curve analyses were used to assess the prognostic differences between participants. Cox regression models were used to estimate the hazard ratios (HRs) for future fracture events among the FL group and non-FL groups in different BMI categories. Non-FL patients with a BMI within the normal range were used as the reference group to compare the HRs. All statistical analyses were performed using the SPSS software (version 29.0.0.0, IBM Corporation, Armonk, NY, USA). All tests were two-sided, and *P*-values less than 0.05 were considered significant.

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Results

Study population and baseline characteristics

Altogether, 941 patients (441 women and 500 men) were included in this study. The average age was 64.88 ± 9.90 (mean ± S.D.) years for women and 66.49 ± 11.20 years for men. The prevalence of FL in women and men was 48.8% (215/441) and 47.6% (238/500), respectively. The overall prevalence of osteoporosis at the time of enrollment was significantly higher in women (29.3%, 127/441) than in men (13.2%, 66/500).

The prevalence of diabetes was significantly higher in female patients with FL (21.4%) compared to those without FL (12.8%) (Table 1, P = 0.023); however, no significant difference was observed between the two groups in male patients. For both men and women, although the proportion of osteoporotic agent use was seemingly slightly higher in the non-FL group than in the FL group, this difference did not reach statistical significance. The proportion of women with hormone HRT or without HRT was also similar in the FL and non-FL groups. As expected, female patients with FL had significantly higher body weight, higher fasting glucose, and triglyceride (TG) levels, and lower high-density lipoprotein cholesterol (HDL-C) levels than female patients without FL (Fig. 2A-1 and Table 2). Similarly, male patients with FL were younger (63.86 ± 10.16 years vs 68.89 ± 11.58 years, P < 0.001), had higher body weight, higher TG levels (<0.001), lower HDL-C levels (<0.001), and higher uric acid and alanine aminotransferase (ALT) levels than male patients with FL (Tables 1, 2 and Fig. 2B-1). A significantly higher prevalence of osteoporosis was observed in patients without FL (19.8% and 17.7% for women and men, respectively) for both sexes, compared to those with FL (12.0% and 8.4%, respectively) (Table 1, P = 0.017 and, 0.003 respectively). More than half (62.8%) of female patients without FL had a normal BMI (18.5 ≤ BMI < 24 kg/m^2). However, more than half (61.6%) of female patients with FL had overweight (24 ≤ BMI < 27 kg/m^2) or obesity (BMI ≥ 27 kg/m^2), and so were the male patients with FL (64.7%). These findings suggested a certain association of FL patients with a higher BMI. The mean body mass index (BMI) was significantly higher in female patients with FL than in those without fatty liver (Fig. 2A-2; FL group: 24.90 ± 4.09 kg/m^2 vs non-FL group: BMI 22.54 ±3 .69 kg/m^2, P < 0.001), and the same could be said for male patients (Fig. 2B-2; FL group: 25.22 ± 3.13 kg/m^2 vs non-FL group: 23.52 ± 3.02 kg/m^2, P < 0.001).

Men with fatty liver had higher hemoglobin (Hgb) levels and a higher prevalence of past fractures (Tables 1 and 2). In both sexes, there were no significant differences in glycated hemoglobin (HbA1c), total cholesterol, low-density lipoprotein cholesterol (LDL-C), aspartate aminotransferase (AST), albumin, renal function (blood urea nitrogen (BUN), creatinine, and estimated glomerular filtration rate (eGFR)), calcium, and phosphorus levels, prevalence of hypertension, current smokers, and current drinkers between those with and without FL fatty liver (Tables 1 and 2).

Table 1 Baseline characteristics of fatty liver (FL) and non-fatty liver (non-FL) patients. Values are presented as number and percentages (%) (in brackets) or mean ± S.D. Differences were tested with Chi-square for categorical variables and with Student's *t* test for numerical data.

	Female			Male		
	FL (n = 215)	Non-FL (n = 226)	P	FL (n = 238)	Non-FL (n = 262)	P
Age (years)	63.48 ± 9.33	66.59 ± 10.72	0.001	63.86 ± 10.16	68.89 ± 11.58	< 0.001
Diabetes	46 (21.4)	29 (12.8)	0.023	55 (23.1)	52 (19.8)	0.436
Hypertension	73 (16.6)	73 (16.6)	0.789	85 (35.7)	100 (38.2)	0.635
Current smoker	3 (1.4)	4 (1.9)	0.660	25 (10.5)	22 (8.4)	0.514
Current drinker	2 (0.9)	2 (0.9)	0.279	29 (12.2)	22 (8.4)	0.211
Osteoporosis (baseline DXA measures)	48 (12.0)	79 (19.8)	0.017	20 (8.4)	46 (17.7)	0.003
Past fracture	39 (18.2)	59 (26.1)	0.061	61 (25.6)	92 (35.1)	0.028
Osteoporosis medications before enrolled	5 (2.3)	6 (2.7)	1.000	3 (1.3)	4 (1.5)	1.000
HRT before enrolled	7 (3.3)	5 (2.2)	0.568	–	–	–
BMI categories (kg/m^2)						
BMI < 18.5	7 (3.3)	18 (8.0)	0.053	4 (1.7)	14 (5.3)	0.051
18.5 ≤ BMI < 24	97 (45.1)	142 (62.8)	< 0.001	80 (33.6)	129 (49.2)	< 0.001
24 ≤ BMI < 27	54 (25.1)	42 (18.6)	0.122	86 (36.1)	88 (33.6)	0.615
BMI ≥ 27	57 (26.5)	24 (10.5)	< 0.001	68 (28.6)	31 (11.8)	< 0.001

BMI, body mass index; FL, fatty liver; HRT, hormone replacement therapy; non-FL, non-fatty liver.

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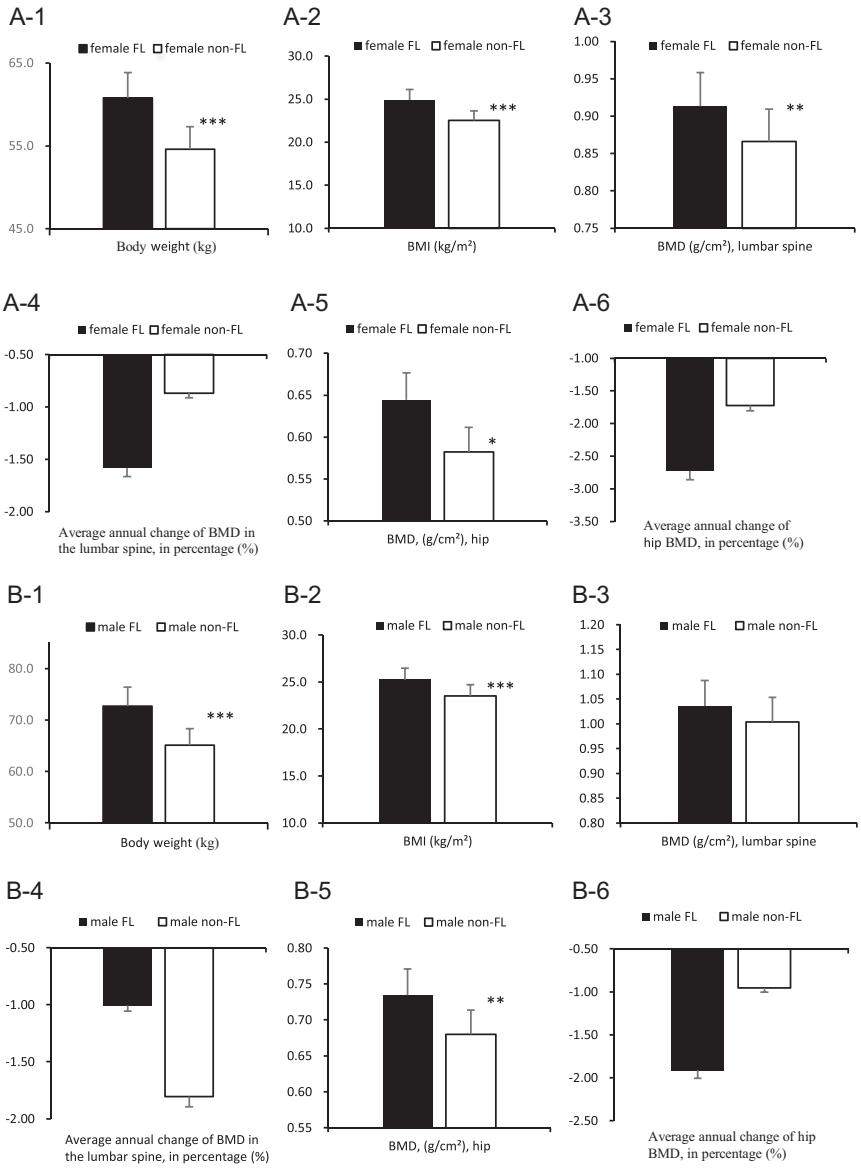

Figure 2

Body weight, body mass index (BMI), and bone mineral density (BMD) of lumbar spine and hip in female and male patients, fatty liver (FL) vs non-fatty liver (non-FL) (A), female; (A-1) body weight (kg); (A-2) BMI (kg/m²); (A-3) BMD (g/cm²), lumbar spine; (A-4) average annual change of BMD in the lumbar spine, in percentage (%); (A-5) BMD (g/cm²), hip; (A-6) average annual change of BMD in the hip, in percentage (%). (B) male; (B-1) body weight (kg); (B-2) BMI (kg/m²); (B-3) BMD (g/cm²), lumbar spine; (B-4) average annual change of BMD in the lumbar spine, in percentage (%); (B-5) BMD (g/cm²), hip; (B-6) average annual change of BMD in the hip, in percentage. *P < 0.05; **P < 0.01; ***P < 0.001.

Age and BMI as independent risk factors for osteoporosis in male and female patients with FL

Figure 2A-3 and A-5 demonstrates that female patients with FL had a significantly higher baseline BMD in the lumbar spine and hip than those without FL. Meanwhile, for male patients with FL, the significance of higher baseline BMD was noted only in the hip and not in the lumbar spine (Fig. 2B-3 and B-5). However, regarding the average annular change in the BMD of the lumbar spine and hip, no significant difference was identified between the patients with and without FL, regardless of sex (Fig. 2A-4, A-6, B-4, B-6).

Female patients without FL had a higher prevalence of osteoporosis (19.8% vs 12.0%, P = 0.017) than female patients with FL (Table 1). A similar finding was also observed in male patients (17.7% vs 8.4% for non-FL and FL patients, respectively, P = 0.003) (Table 1). We conducted logistic regression analysis for variables with significant differences between the FL and non-FL groups of female and male patients (Tables 1 and 2). The univariate analysis suggested that FL, age, and BMI were predictors of osteoporosis in both sexes. In the multivariate analysis, only age and BMI were identified as independent risk factors for osteoporosis for all patients (Table 3).

Patients with FL have better future FFS than those without FL

There were 73 fractures in 441 women and 69 fractures in 500 men. In women, the most common fracture site was the spine (lumbar, thoracic or both) (47 out of

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Table 2 Serological and laboratory data of fatty liver (FL) and non-fatty liver (non-FL) patients. Values are presented as mean ± S.D. Differences were tested with Student's *t*-test.

	Female			Male		
	FL (*n* = 215)	Non-FL (*n* = 226)	*P*	FL (*n* = 238)	Non-FL (*n* = 262)	*P*
Triglycerides (mg/dL)	131.26 ± 62.04	103.07 ± 35.36	<0.001	140.26 ± 27.17	105.44 ± 57.91	<0.001
Total cholesterol (mg/dL)	200.35 ± 32.02	201.00 ± 34.45	0.838	189.53 ± 32.86	184.30 ± 30.26	0.065
HDL-C (mg/dL)	56.55 ± 8.13	60.88 ± 12.30	<0.001	45.58 ± 9.90	50.84 ± 12.22	<0.001
LDL-C (mg/dL)	123.20 ± 26.56	119.30 ± 27.33	0.128	116.78 ± 30.20	113.67 ± 25.08	0.213
Fasting glucose (mg/dL)	108.84 ± 27.56	101.80 ± 22.82	0.003	103.92 ± 18.86	103.99 ± 23.49	0.974
HbA1c (%)	6.23 ± 0.7052	6.08 ± 0.86	0.053	6.07 ± 0.86	5.99 ± 0.75	0.283
Calcium (mg/dL)	10.13 ± 7.07	9.99 ± 2.86	0.778	9.43 ± 0.41	9.65 ± 5.24	0.518
Phosphorus (mg/dL)	3.87 ± 0.27	3.86 ± 0.39	0.826	3.39 ± 0.59	3.33 ± 0.33	0.215
BUN (mg/dL)	15.42 ± 6.76	15.55 ± 7.13	0.849	16.18 ± 6.74	16.87 ± 7.24	0.269
Creatinine (mg/dL)	0.82 ± 0.58	0.98 ± 1.15	0.064	1.01 ± 0.37	1.02 ± 0.34	0.770
eGFR (mL/min/1.73 m^2)	79.15 ± 16.69	77.169 ± 22.00	0.282	80.68 ± 18.36	79.31 ± 20.14	0.429
Uric acid (mg/dL)	5.35 ± 1.04	5.11 ± 1.05	0.020	6.58 ± 1.43	6.00 ± 1.32	<0.001
ALT (U/L)	26.99 ± 27.16	22.00 ± 17.13	0.020	30.77 ± 18.01	23.62 ± 12.72	<0.001
AST (U/L)	25.56 ± 21.23	24.94 ± 15.09	0.720	26.19 ± 12.89	25.79 ± 12.69	0.723
Albumin (mg/dL)	4.71 ± 3.60	4.40 ± 0.36	0.198	4.43 ± 0.31	4.60 ± 5.57	0.650
Hemoglobin (g/dL)	12.73 ± 1.74	12.59 ± 1.55	0.375	14.62 ± 1.48	13.41 ± 2.00	<0.001

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; FL, fatty liver; HbA1c, glycated hemoglobin; HDL-C, high densityhigh-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-FL, non-fatty liver.

73 fractured women, 64.4%), followed by the humerus (7 women, 9.6%) and radius (6 women, 8.2%). In men, the most common sites of fractures were fractures of the spine (lumbar, thoracic, or both) (50 out of 69 fractured men, 72.5%), followed by the ribs (7 men, 10.1%) and the hip (4 men, 5.8%). In male patients, a significant difference in future FFS (P = 0.01 by log-rank test; HR = 0.52; 95% CI: 0.32–0.86) was observed in the FL group compared with the non-FL group (Fig. 3D). Although the difference was not significant for the two groups of female patients, a trend (P = 0.09; HR = 0.66 with 95% CI: 0.41–1.07) of difference in future FFS was still observed between female patients with and without FL (Fig. 3A).

Protective effect of higher BMI against the risk of future fractures in patients with FL diminishes beyond a certain BMI range

For both female and male patients, non-FL patients with a BMI between 18.5 and 24 kg/m^2 were set as the reference group. Women with FL and with a BMI between 24 and 27 kg/m^2 had a significantly lower risk of developing future fractures before and after adjustment for age (HR = 0.33 (95% CI: 0.11–0.93) and HR = 0.32 (95% CI: 0.11–0.91), respectively) (Fig. 3B-1 and B-2).

In male patients, the risks for future fracture were significantly lower in the FL group with a BMI between

Table 3 Factors associated with osteoporosis among female and male patients by logistic regression. A logistic regression model was used to analyze the odds ratios of osteoporosis in female and male patients. In the adjusted model, adjustments were made for age, BMI, TG, HDL-C, uric acid, and ALT.

	Females				Males			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*P*	AOR (95% CI)	*P*	OR (95% CI)	*P*	AOR (95% CI)	*P*
Fatty liver	0.54 (0.35–0.82)	0.003	0.847 (0.520–1.382)	0.507	0.43 (0.25–0.75)	0.002	0.77 (0.41–1.46)	0.427
Age (years)	1.07 (1.05–1.10)	<0.001	1.08 (1.05–1.11)	<0.001	1.08 (1.05–1.11)	<0.001	1.07 (1.04–1.09)	<0.001
BMI (kg/m^2)	0.90 (0.85–0.91)	<0.001	0.89 (0.83–0.95)	<0.001	0.75 (0.68–0.82)	<0.001	0.79 (0.71–0.88)	<0.001
TG (mg/dL)	1.00 (0.99–1.00)	0.137	1.00 (0.99–1.00)	0.281	1.00 (0.99–1.00)	0.069	1.00 (0.99–1.01)	0.915
HDL-C (mg/dL)	1.00 (0.98–1.02)	0.693	1.00 (0.97–1.02)	0.649	1.01 (0.99–1.03)	0.362	1.00 (0.98–1.03)	0.767
Uric acid (mg/dL)	0.94 (0.77– 1.16)	0.558	0.99 (0.79–1.23)	0.892	0.84 (0.70–1.02)	0.084	1.00 (0.98–1.02)	0.905
ALT (U/L)	1.00 (0.99–1.01)	0.557	1.00 (0.99–1.01)	0.717	0.97 (0.95–1.00)	0.035	0.99 (0.79–1.22)	0.889

ALT, alanine amino transferase aminotransferase; AOR, adjusted OR; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio; TG, triglycerides.

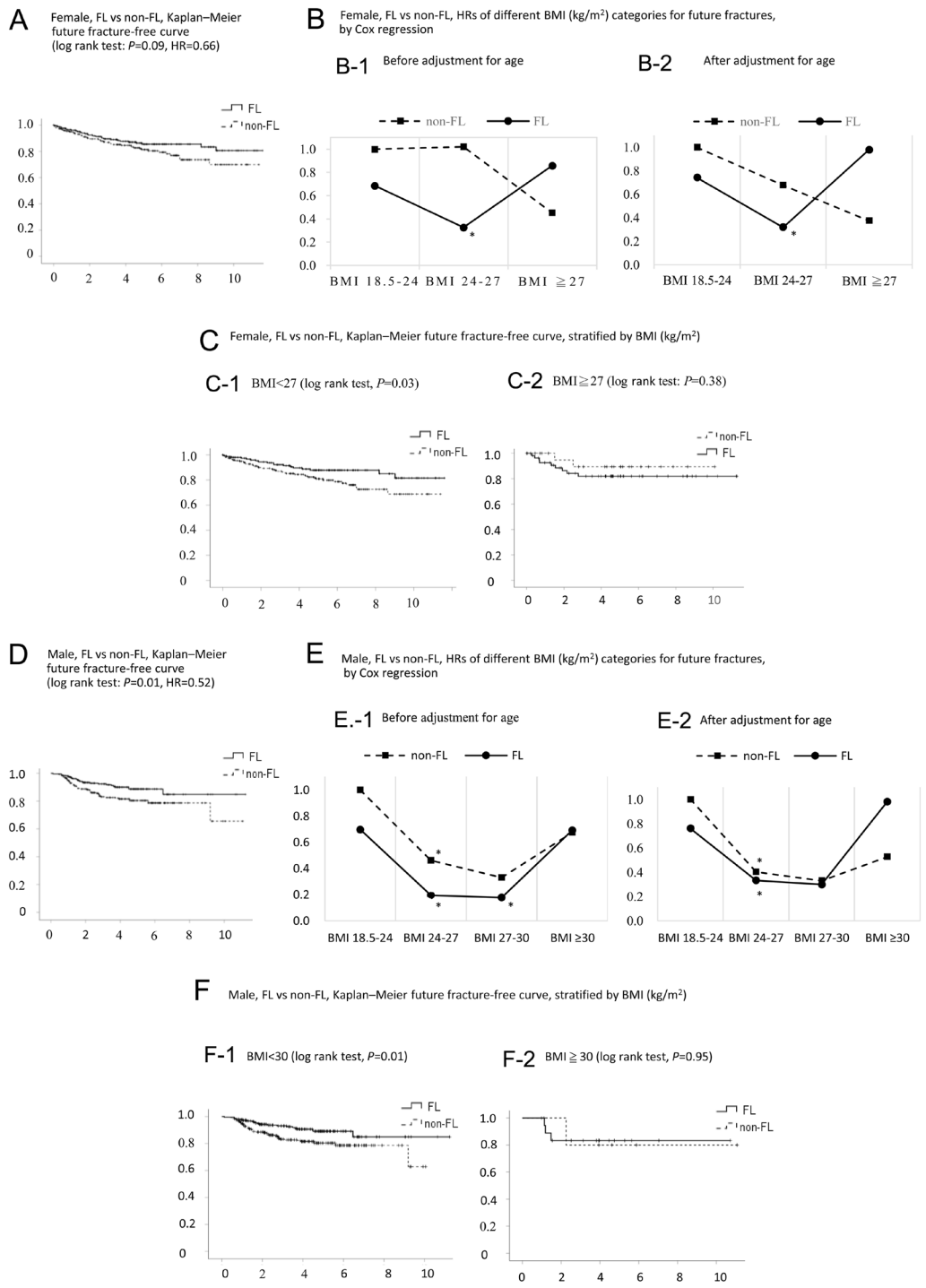

Figure 3

Kaplan–Meier future fracture-free curve in female and male patients, with and without fatty liver (FL and non-FL), and hazard ratios (HRs) for future fractures of different body mass index (BMI) categories. (A) Kaplan–Meier future fracture-free curve for all female patients; (B) HRs of developing future fractures for different BMI (kg/m²) categories in female patients by Cox regression, with non-FL women with a BMI 18.5–24 as the reference group; (B-1) before adjusting for age; (B-2) after adjusting for age; (C) Kaplan–Meier future fracture-free curve for female patients, stratified by BMI (kg/m²); (C-1) BMI < 27; (C-2) BMI ≥ 27; (D) Kaplan–Meier future fracture-free curve for all male patients; (E) HRs of developing future fractures for different BMI (kg/m²) categories in male patients by Cox regression, and non-FL men with a BMI 18.5–24 as the reference group; (E-1) before adjusting for age; (E-2) after adjusting for age; (F) Kaplan–Meier future fracture-free curve for male patients, stratified by BMI (kg/m²); (F-1) BMI < 30; and (F-2) BMI ≥ 30.
*P < 0.05 vs non-FL group with a BMI 18.5–24.

24 and 27 kg/m^2 (HR = 0.19 (95% CI, 0.07–0.55)) and a BMI between 27 and 30 kg/m^2 (HR = 0.18 (95% CI: 0.04–0.74)) before adjusting for age (Fig. 3E-1). However, after adjusting for age, only a BMI between 24 and 27 kg/m^2 persisted to decrease the risk of future fracture (HR = 0.33 (95% CI: 0.12–0.96) (Fig. 3E-1 and E-2).

If female patients were stratified using BMI = 27 kg/m^2 as the cutoff point, the results revealed that a BMI of <27 kg/m^2 would affect their FFS. Female patients with FL had better FFS than those without FL with a BMI of <27 kg/m^2 (log-rank test, P = 0.03) (Fig. 3C-1). FFS revealed no significant difference between patients with and without FL with a BMI of ≥27 kg/m^2 (Fig. 3C-2). This was also observed in male patients (BMI < 30 kg/m^2, P = 0.01; BMI ≥ 30 kg/m^2, P = 0.95) (Fig. 3F). The abovementioned data suggest that patients with FL and a BMI between 24 and 27 might have a lower risk of future fractures than those without FL and with a normal BMI. However, this effect was diminished for women with a BMI of ≥27 kg/m^2 and men with a BMI ≥ 30 kg/m^2.

Discussion

Patients with FL are at a higher risk of developing a combination of metabolic disorders (such as high BMI or obesity, elevated ALT levels, elevated fasting glucose levels, dyslipidemia, and hyperuricemia) (18). As expected, our study demonstrated higher BMI, elevated serum levels of TG, uric acid, and ALT, and lower HDL-C in the FL group than in the non-FL group in both sexes.

Osteoporosis is considered to lead to an increased risk of future fractures. Past studies have shown that in addition to BMI, serum TG, uric acid, HDL-C, and liver enzymes were associated with the risk of osteoporosis (19, 20, 21, 22). In our study, the prevalence of osteoporosis was lower in female and male patients with FL than in those without FL. In the study population, no significant associations were identified between osteoporosis and serum TG, uric acid, HDL-C, or ALT levels in the multivariate analysis. Age and BMI were the only independent predictors of osteoporosis in both sexes. Each unit increase in BMI would decrease the risk of osteoporosis by approximately ≥10% (OR = 0.90 (95% CI, 0.85–0.91) in women and OR = 0.75 (95% CI: 0.679–0.824) in men). Similar to other studies (9, 23, 24), a higher BMI protects against osteoporosis, and a low BMI could be a risk factor for osteoporosis.

A high BMI has been associated with a lower risk of fractures of the hip, spine, and wrist in postmenopausal women (11, 25, 26). In our study, a higher BMI was strongly correlated with FL for both women and men. However, only in men, the Kaplan–Meier future fracture-free curve demonstrated a significantly reduced fracture risk in the FL group compared to the non-FL group. In this study, the distribution of diabetes was comparable between the FL and non-FL groups of men. But in women, the fatty liver group exhibited a higher proportion of diabetes than the non-fatty liver group (Table 1). Diabetes has been identified as a risk factor for fractures (27). The unequal distribution of diabetes among the FL and non-FL groups may have influenced the observation of the interaction between fatty liver and future fractures in women. This may be a confounding factor to the observation that no significant difference (P = 0.09, Fig. 3A) in fracture risk between the fatty liver and non-fatty liver groups by Kaplan–Meier future fracture-free curve. Moreover, the highest level of BMI did not translate into the greatest reduction in the risk of fracture. By investigating the synergistic effect of FL and BMI on the susceptibility to future fractures, an aspect less explored in extant literature, we identified the optimal BMI range for reducing the risk of future fractures in patients with FL. This study preliminarily suggests that both women and men with FL who maintain a BMI between 24 and 27 kg/m^2 have the greatest risk reduction for future fractures.

The risk association of fractures showed a nonlinear pattern according to BMI (8, 28). A recent study has demonstrated that an excessively high BMI was detrimental to BMD in the elderly (29). Concurrently, elevated BMI also contributes to progression or comorbidities of fatty liver (30). In men with or without FL in our study, the risk of future fractures seemed to increase with a BMI > 30, especially in those with FL (Fig. 3E-2). This is compatible with the 'U' shape relationship of the risk of fracture and high BMI (31). However, this pattern for the risk of future fracture according to BMI was observed in women with FL, not in women without FL.

Our retrospective cohort study, conducted between 2011 and 2019, aimed to investigate the combined effect of FL and BMI on future fracture risk, a topic that has been relatively underinvestigated in prior research. To this end, we performed a sex-specific analysis to evaluate the interactions between these variables. The findings indicated that the association among these variables was modulated by distinct BMI categories. There were some limitations about our study. Given the multitude of personal and clinical factors that influence bone mineral density and fracture risk, we initially excluded certain variables from the case collection and included others in the analysis. However, some variables, including frailty, height loss of more than 4 cm, or parental history of hip fracture, could not be identified from the medical records. Additionally, the study was conducted at a tertiary referral center with a limited ethnic diversity. This may limit the generalizability of the findings to other populations.

In conclusion, these data may reveal the overall trends in fracture risk influenced by different ranges of BMI in the presence of FL and identify a potential optimal BMI threshold for fracture prevention in the context of fatty liver disease. Although the statistical

analysis suggests a possible interaction between FL and BMI on fracture risk, further investigation and possibly more data may be required to draw firm conclusions on the clinical significance of this finding.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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Ethical approval

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (2022-13-010BCF and 2023-08-018BC). The informed consent was exempted for this minimal risk research by the Institutional Review Board of Taipei Veterans General Hospital. This study was performed in accordance with the Declaration of Helsinki.

Informed consent

The Institutional Review Board of Taipei Veterans General Hospital exempted informed consent for this minimal risk research.

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