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Low geriatric nutritional risk index is associated with osteoporosis and fracture risk in patients with chronic liver disease: a cross-sectional study

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Abstract

Background Patients with chronic liver disease (CLD) frequently suffer from malnutrition and bone diseases, both of which heighten the risk of poor clinical outcomes. This study investigated the relationship between geriatric nutritional risk index (GNRI) and osteoporosis or fracture risk using the fracture risk assessment tool (FRAX) in patients with CLD.

Methods This cross-sectional study included 209 consecutive patients with CLD. The participants were divided into two groups: the all-risk group (GNRI ≤ 98.0) with nutrition-related risk and the no-risk group (GNRI > 98.0) without nutrition-related risk. Osteoporosis was diagnosed according to the World Health Organization criteria. The FRAX was used to estimate the 10-year probabilities of hip fracture (FRAX-HF) and major osteoporotic fracture (FRAX-MOF).

Results Of the 209 patients, 72 (34.4%) had osteoporosis. The all-risk group had a significantly higher prevalence of osteoporosis than the no-risk group ($p < 0.001$). Conversely, patients with osteoporosis had significantly lower GNRI than those without osteoporosis ($p < 0.001$). Multivariate analysis found lower GNRI to be a significant and independent risk factor for osteoporosis (odds ratio [OR], 0.927; $p < 0.001$) and high fracture risk derived from FRAX (without BMD) (OR, 0.904; $p = 0.009$). GNRI had a positive correlation with bone mineral density (BMD) at the lumbar spine, femoral neck, and total hip, but a negative correlation with FRAX-HF and FRAX-MOF in the FRAX with and without BMD ($p < 0.001$ for all). The cutoff value of GNRI for predicting osteoporosis was 104.9, with sensitivity of 0.667 and specificity of 0.657.

Conclusions The GNRI was significantly associated with osteoporosis and FRAX-derived fracture risk in patients with CLD, suggesting that it could be a simple and useful indicator for the management of bone diseases.

Keywords Chronic liver disease, Geriatric nutritional risk index, Osteoporosis, Fracture risk

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Background

Osteoporosis is a systemic bone disease characterized by reduced bone mass and deterioration of bone microarchitecture [1]. In patients with chronic liver disease (CLD), osteoporosis is one of the most common extrahepatic comorbidities [2–4]. Furthermore, patients with CLD are susceptible to fragility fracture due to reduced bone mass and impaired bone quality [5]. A meta-analysis revealed that patients with cirrhosis have a higher prevalence of osteoporosis than controls (odds ratio [OR], 2.52) [6]. Another meta-analysis found that patients with CLD have a higher risk of osteoporotic fractures than those without CLD (pooled OR, 2.13) [7]. Such situations are attributed to many factors, such as hyperbilirubinemia, imbalance of the receptor activator of nuclear factor kappa-B ligand/osteoprotegerin ratio, vitamin D deficiency, decreased insulin-like growth factor 1 level, increased proinflammatory cytokine (e.g., tumor necrosis factor-alpha [TNF-α], interleukin [IL]-6, and IL-1) levels, and increased sclerostin level [2–4]. Moreover, malnutrition, which is common in patients with cirrhosis, is linked to an increased risk of osteoporosis and subsequent fragility fractures [8–11]. However, few detailed studies have focused on the impact of malnutrition or nutritional status on these bone diseases in patients with CLD. Since osteoporosis and fragility fractures are associated with negative clinical outcomes (such as renal failure, infections, and mortality) especially in patients with cirrhosis and postmenopausal women [12–14], early evaluation and therapeutic intervention for bone diseases are critical to preventing these events. However, proper assessment of bone diseases and malnutrition remains inadequate because of the difficulty in quantification and lack of clinical practice guidelines for osteoporosis and malnutrition specific to CLD in real-world clinical settings.

The geriatric nutritional risk index (GNRI), which is calculated using present/ideal body weight and serum albumin levels, was advocated to estimate the risk of malnutrition-related morbidity and mortality in elderly patients [15]. This nutritional index categorizes subjects into four nutrition-related risk groups (i.e., no-, low-, moderate-, and major-risk groups). Recent research has found that low GNRI is associated with decreased bone mineral density (BMD) and osteoporosis in patients with diabetes mellitus, rheumatoid arthritis (RA), and postmenopausal women [16–20]. In a previous study of patients undergoing hemodialysis, low GNRI increased a bone fracture risk [21]. Thus, the GNRI could be a simple and useful indicator for estimating osteoporosis and fracture risk, as well as malnutrition-related morbidity and mortality.

The fracture risk assessment tool (FRAX), which comprises 12 items (such as age, sex, previous fracture, and the presence of diseases that cause secondary osteoporosis), is a well-established online algorithm for estimating the 10-year probabilities of major osteoporotic and hip fractures [22]. Since its establishment by the World Health Organization (WHO) in 2008, the FRAX models are currently available in 78 countries, reaching more than 80% of the global population [23]. However, it is unclear how malnutrition (e.g., as measured by the GNRI) affects the FRAX-derived fracture risk.

Given the high prevalence and clinical significance of bone diseases (osteoporosis and fractures) and the impact of malnutrition/nutrition status on such diseases in patients with CLD, a simple and convenient screening indicator for the risk of these comorbidities is advantageous in routine clinical practice where medical resources and time/effort are limited. This study aimed to determine whether GNRI-assessed nutritional status could be used to predict these bone-related events, as well as the relationship between GNRI, osteoporosis, and FRAX-derived fracture risk.

Methods

This cross-sectional study was conducted at Fuji City General Hospital (Shizuoka, Japan) and the Jikei University School of Medicine (Tokyo, Japan) from May 2017 to August 2020 and enrolled 209 consecutive outpatients with CLD. The inclusion criteria were as follows: (1) patients with CLD aged 40–90 years who met the recommendation of the FRAX and (2) availability of BMD measurements. The exclusion criteria were as follows: (1) alcoholic liver disease resulting from heavy alcohol intake (>3 units/day), which causes severe malnutrition and (2) patients with ascites, which causes weight gain and overestimation of GNRI scores. Medical records and questionnaires were used to survey body height and weight, current smoking and alcohol intake status, family and previous history of fracture, RA complications, and glucocorticoid use. Serum creatinine, albumin, total bilirubin, and prothrombin time (PT) were measured using standard laboratory methods. Mac-2 binding protein glycosylation isomer (M2BPGi, a hepatic fibrosis marker) was measured using a sandwich enzyme-linked immunosorbent assay with Wisteria floribunda lectin-recognizing carbohydrate chains (HISCL-2000i; Sysmex, Hyogo, Japan), and the results were presented as a cutoff index (C.O.I.) converted using the manufacturer's specified formula. The estimated glomerular filtration rate (eGFR) was calculated using the following formula: eGFR (mL/min/1.73 m^2) = 194 × creatinine $^{-1.094}$ × age $^{-0.287}$ (× 0.739 for women). This study was designed and conducted following the 2013 Declaration of Helsinki and was approved by the ethics committees of Fuji City General Hospital (Approval no. 162) and the Jikei University

School of Medicine (Approval no. 28–194). All participants provided written informed consent.

Osteoporosis and fracture assessment

BMD at the lumbar spine (L2–L4), femoral neck, and total hip was evaluated using dual-energy X-ray absorptiometry (PRODIGY; GE Healthcare Japan, Tokyo, Japan). Osteoporosis was diagnosed using the WHO criteria: T-score ≤ −2.5 [24]. All participants underwent lateral thoracolumbar spine radiography at the time of study entry and were assessed for prevalent vertebral fractures using the Genant's semi-quantitative method [25]. Prevalent fractures were defined as those that occurred in the past but have not yet healed or have left traces at the time of study entry.

Fracture risk assessment with the FRAX

Fracture risk was estimated using the FRAX recommended by the WHO [22]. FRAX scores (%) were calculated as the 10-year probabilities of hip fracture (FRAX-HF) and major osteoporotic fracture (FRAX-MOF) using the Japanese version of FRAX with and without BMD (https://www.sheffield.ac.uk/FRAX/tool.aspx?country=3). High fracture risk was defined as FRAX-HF ≥ 3% or FRAX-MOF ≥ 20% [26].

Classification based on the GNRI score

The GNRI was calculated with the present/ideal body weight and serum albumin levels using the following formula: GNRI = (14.89 × albumin [g/dL]) + (41.7 × [present body weight/ideal body weight]) [15]. The original GNRI classified subjects into four risk categories: no risk (> 98), low risk (92 to ≤ 98), moderate risk (82 to < 92), and major risk (< 82) [15]. In this study, the participants were divided into two groups based on the original GNRI classification and previous studies [15, 27, 28]: the all-risk group (GNRI ≤ 98.0) with nutrition-related risk and the no-risk group (GNRI > 98.0) without nutrition-related risk.

Statistical analysis

Continuous variables are presented as medians (interquartile ranges), and the Mann–Whitney U test was used to compare between-group differences. Categorical variables are presented as numbers (percentages), and the chi-squared test was used to compare between-group differences. Univariate logistic regression analysis was initially used to identify osteoporosis-related factors with $p < 0.10$. Subsequently, multivariate analysis (excluding body mass index [BMI] and albumin, both of which were GNRI components) was used to identify independent risk factors for osteoporosis. The Spearman's rank correlation test was used to investigate correlations between the GNRI and continuous variables. The area under the receiver operating characteristic curve of the GNRI was calculated to determine the most optimal cut-off value for predicting osteoporosis. All statistical analyses were carried out using SPSS Statistics version 27 (IBM Japan, Tokyo, Japan). Values of $p < 0.05$ were considered statistically significant.

Results

Patient characteristics

Table 1 presents the baseline clinical characteristics of the 209 enrolled patients. This study cohort comprised 84 (40.2%) men and 125 (59.8%) women, with a median age of 70.0 (59.0–76.0) years. The median GNRI score was 106.0 (99.9–112.1). The prevalences of cirrhosis and osteoporosis were 35.9% (75/209) and 34.4% (72/209), respectively. There were 62 (29.7%) patients with prevalent fractures, including vertebrae ($n = 52$ [symptomatic, $n = 27$; asymptomatic, $n = 25$]), proximal humerus ($n = 1$) and femur ($n = 6$), distal radius ($n = 7$), ribs ($n = 6$), lower extremity ($n = 5$), and pelvis ($n = 4$).

Clinical characteristics of the all-risk and no-risk groups

The percentages of patients in the all-risk and no-risk groups were 19.1% (40/209) and 80.9% (169/209), respectively (Table 1). The all-risk group was older ($p = 0.015$), had higher levels of M2BPGi ($p < 0.001$), lower levels of PT ($p = 0.031$) and BMD at the femoral neck ($p = 0.039$) and total hip ($p = 0.003$) than the no-risk group. Notably, the prevalence of osteoporosis in the all-risk group was significantly higher than that in the no-risk group (55.0% vs. 29.6%; $p = 0.002$). Meanwhile, the GNRI scores in patients with osteoporosis were significantly lower than those without it ($p < 0.001$; Figure S1).

Correlations between GNRI and BMD

GNRI showed a significant and positive correlation with BMD at the lumbar spine ($r = 0.268$), femoral neck ($r = 0.350$), and total hip ($r = 0.410$) ($p < 0.001$ for all; Fig. 1).

Significant factors related to osteoporosis

Univariate analysis found the following seven variables to be significant risk factors for osteoporosis: male gender, age, cirrhosis, eGFR, M2BPGi, GNRI, and prevalent fracture (Table S1). Multivariate analysis found male gender (OR, 0.252; 95% confidence interval [CI], 0.113–0.561; $p < 0.001$), advanced age (OR, 1.080; 95%CI, 1.035–1.127; $p < 0.001$), lower GNRI (OR, 0.927; 95%CI, 0.888–0.967; $p < 0.001$), and prevalent fracture (OR, 4.582; 95%CI, 2.089–10.047; $p < 0.001$) to be independent risk factors for osteoporosis in patients with CLD (Table 2).

Table 1 Comparison of clinical characteristics between the all-risk and no-risk groups

Variable	All patients	All-risk	No-risk	*p* value
Patients, n (%)	209	40 (19.1)	169 (80.9)	
Men/Women, n (%)	84 (40.2)/125 (59.8)	17 (42.5)/23 (57.5)	67 (39.6)/102 (60.4)	0.741
Age (years)	70.0 (59.0–76.0)	73.0 (67.5–77.8)	69.0 (58.0–76.0)	0.015
BMI (kg/m^2)	23.1 (20.9–26.1)	20.2 (18.9–22.0)	23.9 (21.7–26.6)	< 0.001
Etiology				
HBV/HCV/PBC/Other, n	43/72/56/38	9/12/14/5	34/60/42/33	0.476
Cirrhosis, n (%)	75 (35.9)	19 (47.5)	56 (33.1)	0.089
Total bilirubin (mg/dL)	0.6 (0.5–0.9)	0.6 (0.4–0.9)	0.7 (0.5–0.9)	0.590
Albumin (g/dL)	4.1 (3.9–4.4)	3.8 (3.5–3.9)	4.2 (4.0–4.4)	< 0.001
Prothrombin time (%)	98 (81–100)	89 (76–100)	99 (83–100)	0.031
Creatinine (mg/dL)	0.78 (0.67–0.97)	0.75 (0.66–0.92)	0.79 (0.67–0.97)	0.746
eGFR (mL/min/1.73m^2)	63 (53–76)	65 (53–78)	62 (53–76)	0.501
M2BPGi (C.O.I.)	1.23 (0.69–2.03)	1.66 (1.32–2.67)	1.07 (0.67–1.76)	< 0.001
GNRI	106.0 (99.9–112.1)	94.3 (90.6–96.9)	108.2 (103.8–113.4)	< 0.001
Lumbar spine BMD (g/cm^2)	1.06 (0.88–1.21)	0.93 (0.87–1.14)	1.07 (0.89–1.23)	0.057
Lumbar spine T score	−0.90 (−2.10–−0.30)	−1.55 (−2.20–−0.24)	−0.60 (−1.90–0.40)	0.073
Femoral neck BMD (g/cm^2)	0.74 (0.66–0.87)	0.70 (0.61–0.84)	0.75 (0.67–0.88)	0.039
Femoral neck T score	−1.90 (−2.58–−1.00)	−2.15 (−2.98–−1.42)	−1.80 (−2.45–−0.91)	0.026
Total hip BMD (g/cm^2)	0.81 (0.69–0.93)	0.72 (0.62–0.88)	0.83 (0.71–0.95)	0.003
Total hip T score	−1.50 (−2.20–−0.60)	−2.11 (−2.50–−1.20)	−1.30 (−1.99–−0.50)	0.001
Osteoporosis, n (%)	72 (34.4)	22 (55.0)	50 (29.6)	0.002
Prevalent fractures, n (%)	62 (29.7)	14 (35.0)	48 (28.4)	0.411
Prevalent vertebral fracture, n (%)	52 (24.9)	14 (35.0)	38 (22.5)	0.100
Asymptomatic, n (%)	25 (48.1)	8 (57.1)	17 (44.7)	0.427

Continuous variables are shown as median (interquartile range). Statistical analysis was performed using the chi-squared test or the Mann-Whitney U test, as appropriate. BMD, bone mineral density; BMI, body mass index; C.O.I., cut-off index; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; HBV, hepatitis B virus; HCV, hepatitis C virus; M2BPGi, Mac-2 binding protein glycosylation isomer; PBC, primary biliary cholangitis

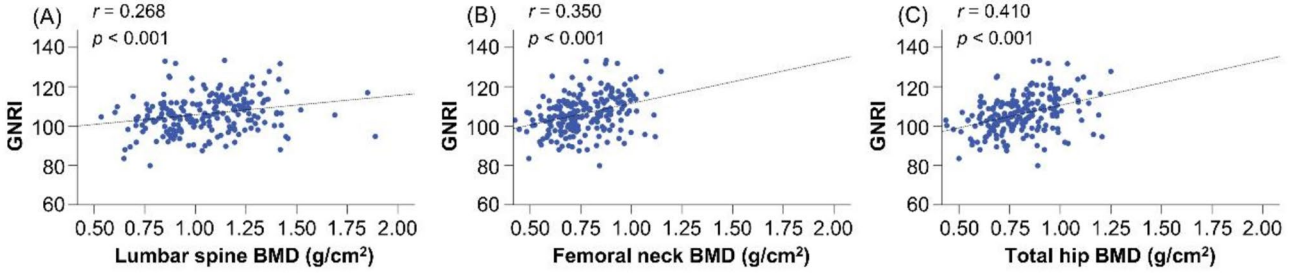


Fig. 1 Correlations between geriatric nutritional risk index (GNRI) and bone mineral density (BMD). GNRI was significantly correlated with BMD at the (**A**) lumbar spine ($r = 0.268$), (**B**) femoral neck ($r = 0.350$), and (**C**) total hip ($r = 0.410$) ($p < 0.001$ for all)

Table 2 Significant factors associated with osteoporosis in patients with chronic liver disease

Variable	Univariate		Multivariate	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Gender (Man)	0.397 (0.213–0.740)	0.004	0.252 (0.113–0.561)	< 0.001
Age (years)	1.107 (1.068–1.149)	< 0.001	1.080 (1.035–1.127)	< 0.001
Cirrhosis	1.749 (0.971–3.150)	0.063		
eGFR (mL/min/1.73m^2)	0.980 (0.963–0.998)	0.028		
M2BPGi (C.O.I)	1.185 (1.000–1.405)	0.050		
GNRI	0.923 (0.890–0.957)	< 0.001	0.927 (0.888–0.967)	< 0.001
Prevalent fracture	7.306 (3.782–14.114)	< 0.001	4.582 (2.089–10.047)	< 0.001

CI, confidence interval; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; M2BPGi, Mac-2 binding protein glycosylation isomer; OR, odds ratio

Optimal cut-off values for age and GNRI for predicting osteoporosis

Figure 2 depicts the cut-off values and diagnostic utility of age and GNRI in predicting osteoporosis. The cut-off values for age and GNRI were 72.5 years [area under the curve (AUC), 0.76; sensitivity, 0.667; specificity, 0.723] and 104.9 (AUC, 0.70; sensitivity, 0.667; specificity, 0.657), respectively (Fig. 2A and B).

Frequency of high fracture risk in the all-risk and no-risk groups

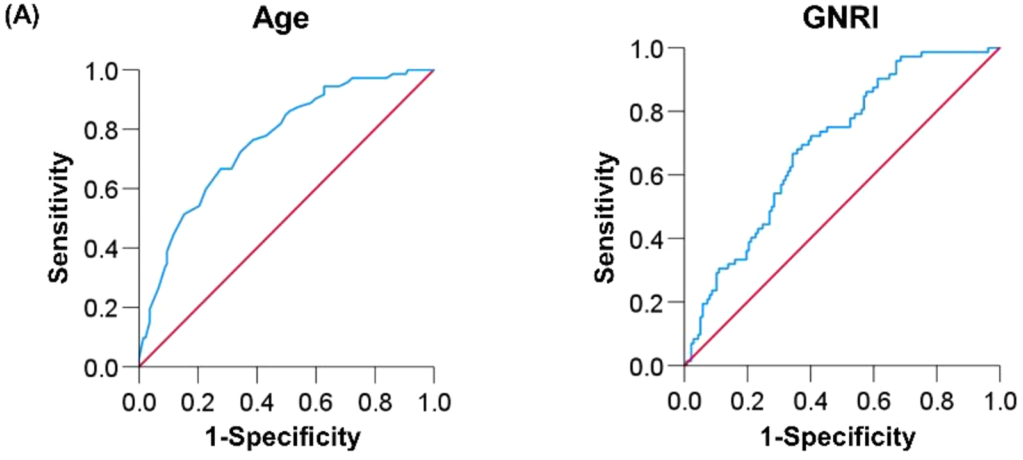
In the assessment using the FRAX with BMD, the FRAX-HF and FRAX-MOF for all participants were 1.9% (0.6–5.5%) and 9.0% (4.9–17.0%), respectively (Table S2). The all-risk group had significantly higher FRAX-HF than the no-risk group (median: 3.4% vs. 1.7%; $p=0.026$). Furthermore, the former had a higher frequency of high fracture risk than the latter, although the difference was marginally significant (52.5% vs. 37.3%; $p=0.077$; Figure S2A). Meanwhile, in the assessment using the FRAX without BMD, FRAX-HF and FRAX-MOF for all patients were 4.5% (1.1–12.0%) and 13.0% (6.7–24.0%), respectively (Table S3). The all-risk group had significantly higher FRAX-HF and FRAX-MOF than the no-risk group (9.2% vs. 3.2%; $p<0.001$, and 18.5% vs. 12.0%; $p=0.006$, respectively). Furthermore, the all-risk group had significantly more high fracture risk than the no-risk group (80.0 vs. 52.7%; $p=0.002$; Figure S2B).

Correlations between GNRI and FRAX scores

In the FRAX with BMD, GNRI was significantly and negatively correlated with FRAX-HF ($r=-0.347$) and FRAX-MOF ($r=-0.277$) ($p<0.001$ for both; Fig. 3A and B). Similarly, in the FRAX without BMD, GNRI was significantly and negatively correlated with FRAX-HF ($r=-0.436$) and FRAX-MOF ($r=-0.345$) ($p<0.001$ for both; Fig. 3C and D).

Significant factors related to high fracture risk assessed using FRAX with and without BMD

In the FRAX with BMD, univariate analysis revealed a significant association between the following variables and high fracture risk: male gender, age, cirrhosis, eGFR, GNRI, prevalent fracture, and osteoporosis (Table S4). Multivariate analysis identified the following significant and independent variables (Table S5): male gender (OR, 0.314; 95% CI, 0.109–0.906; $p=0.032$), advanced age (OR, 1.197; 95%CI, 1.112–1.288; $p<0.001$), prevalent fracture (OR, 5.699; 95%CI, 2.099–15.470; $p<0.001$), and osteoporosis (OR, 15.635; 95%CI, 5.538–44.138; $p<0.001$). In the FRAX without BMD, univariate analysis revealed a significant association between the following variables and high fracture risk: age, cirrhosis, eGFR, GNRI, and



(B)

Variable	AUC	Cutoff value	Sensitivity	Specificity	PPV	NPV
Age (years)	0.76	72.5	0.667	0.723	0.558	0.805
GNRI	0.70	104.9	0.667	0.657	0.505	0.789

Fig. 2 The receiver operating characteristic curve analysis of age and geriatric nutritional risk index (GNRI) for predicting osteoporosis. (**A**) The cutoff value for age was 72.5 years, with an area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 0.76, 0.667, 0.723, 0.558, and 0.805, respectively. (**B**) The cutoff value for GNRI was 104.9, with an AUC, sensitivity, specificity, PPV, and NPV of 0.70, 0.667, 0.657, 0.505, and 0.789, respectively

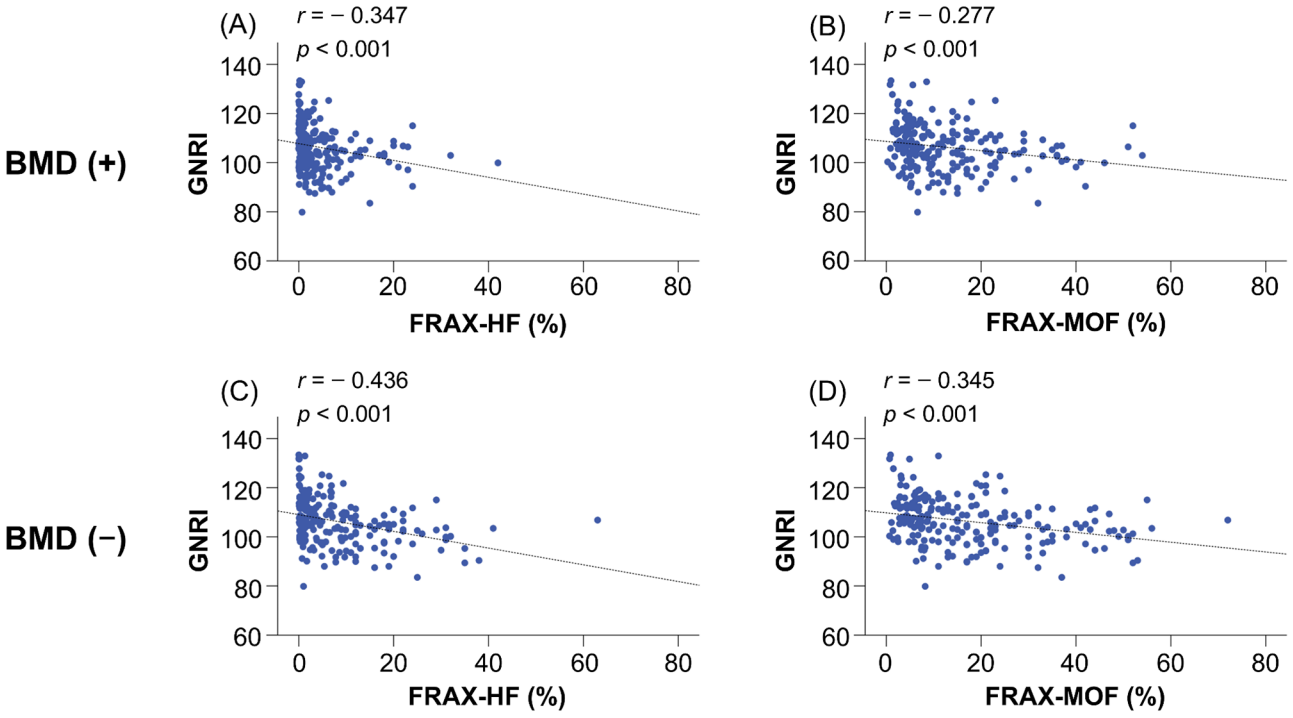


Fig. 3 Correlations between geriatric nutritional risk index (GNRI) and 10-year probabilities of hip fracture (FRAX-HF) and major osteoporotic fracture (FRAX-MOF). (**A**) (**B**) In the FRAX with mineral density (BMD), GNRI was significantly correlated with FRAX-HF ($r = -0.347$) and FRAX-MOF ($r = -0.277$) ($p < 0.001$ for both). (**C**) (**D**) In the FRAX without BMD, GNRI was significantly correlated with FRAX-HF ($r = -0.436$) and FRAX-MOF ($r = -0.345$) ($p < 0.001$ for both). FRAX, fracture risk assessment tool

prevalent fracture (Table S6). Multivariate analysis identified the following significant and independent variables (Table S7): advanced age (OR, 1.666; 95%CI, 1.375–2.020; $p < 0.001$), lower GNRI (OR, 0.904; 95%CI, 0.838–0.975; $p = 0.009$), and prevalent fracture (OR, 58.696; 95%CI, 4.471–770.590; $p = 0.002$).

Discussion

Malnutrition, osteoporosis, and fragility fractures are serious comorbidities in patients with CLD, given that they increase the risk of hepatic complications (including ascites, encephalopathy, hepatorenal syndrome, and spontaneous bacterial peritonitis) and mortality [12, 14, 29, 30]. However, early and comprehensive risk assessment of these extrahepatic clinical events remains inadequate in real-world clinical settings. Recent research has demonstrated that the GNRI is related to osteoporosis and fracture risk in certain physiological and disease states, including type 2 diabetes, RA, ongoing hemodialysis, and postmenopausal status [16–21]. In one study of patients with type 2 diabetes, GNRI was positively correlated with BMD and independently related to osteoporosis, with a cutoff value of 99.56 predicting osteoporosis [17]. In another study of postmenopausal women, GNRI was positively associated with BMD at the femur and negatively associated with osteoporosis risk [20]. In another study of patients undergoing hemodialysis, low GNRI independently related to an increased risk of bone fractures [21]. In the other study of patients who underwent percutaneous vertebroplasty for osteoporotic vertebral fractures, the GNRI was useful for predicting subsequent vertebral fractures [31]. The present study is the first to focus on the relationship between GNRI and osteoporosis or FRAX-derived fracture risk in patients with CLD. As a result, the all-risk group had higher rates of osteoporosis and high fracture risk than the no-risk group. GNRI was positively correlated with BMD but negatively correlated with FRAX-HF and FRAX-MOF. Moreover, multivariate analysis identified lower GNRI as a significant and independent risk factor for osteoporosis and FRAX (without BMD)-derived high fracture risk.

Patients with CLD frequently experience malnutrition caused by various factors, including impaired macro-/micronutrients intake, malabsorption, hypermetabolism, decreased hepatic glycogen stores and synthesis, decreased branched-chain amino acids due to glutamine synthesis and ammonia clearance, and elevated inflammatory cytokine levels [9, 32, 33]. In a previous study of cirrhotic transplant candidates, malnutrition, as assessed by anthropometry (such as triceps skinfold, mid-arm muscle circumference, BMI, and weight loss during the past 3 or 6 months), was closely related to osteopenia and osteoporosis. Furthermore, baseline TNF-α (systemic inflammation marker) levels were associated with

BMD decrease post-liver transplantation [8]. Reportedly, GNRI was inversely correlated with inflammatory markers, such as IL-6 and C-reactive protein in patients with chronic kidney disease and older inpatients [34, 35], implying that GNRI may also reflect chronic inflammatory conditions. Serum levels of proinflammatory cytokines, like IL-1β, IL-6, and TNF-α, were reported to be elevated in patients with CLD, especially those with cirrhosis [36]. In chronic inflammatory conditions, elevated levels of proinflammatory cytokines promote osteoclast activation and bone resorption, resulting in bone loss [4, 37]. Furthermore, malnutrition and inflammatory conditions can reduce the levels of insulin-like growth factor 1 (IGF-1), which is produced primarily in the liver and plays a pivotal role in bone formation and maintenance [38–41]. In our previous study, decreasing serum IGF-1 levels were related to increasing osteoporosis prevalence and FRAX-derived fracture risk in patients with primary biliary cholangitis [42]. Thus, these findings suggested that the GNRI, which estimates malnutrition-related complications and may reflect inflammatory conditions, could be a simple and useful indicator for predicting osteoporosis and fracture risk in patients with CLD.

In this study cohort, the cutoff value of GNRI for predicting osteoporosis was 104.9, which was higher than that of the original GNRI classification [15]. This discrepancy may arise from the following: (1) the original cohort's median age was higher than ours (83.8 vs. 70.0 years), and (2) given that the liver has multiple functions such as nutrient metabolism and hormonal regulation, impaired liver function results in lower vitamin D, IGF-1, and testosterone levels [4]. Patients with CLD may be more susceptible to osteoporosis due to various factors other than malnutrition, compared with individuals without liver diseases, which would raise the GNRI cutoff value. However, screening with this GNRI cutoff value may be helpful for early diagnosis and therapeutic interventions for osteoporosis, leading to fracture prevention.

In this study, both prevalent fractures and low GNRI were found to be significant independent predictors of FRAX-derived high fracture risk. Reportedly, the presence of prevalent fractures at any sites increases the risk of future fractures [43]. For example, patients with a history of prevalent vertebral fractures had a 4.4- and 2.2-fold higher risk of subsequent vertebral and hip fractures, respectively, than those without prevalent fractures. We previously reported that CLD patients with prevalent fractures had higher prevalence of osteoporosis and poorer bone quality than those without [5]. Fractures also increase the risk of reduced physical performance, frailty, and falls, all of which can cause future fractures [44]. Therefore, patients with CLD should be closely monitored for future fractures, especially those with prevalent fractures and/or low GNRI.

Malnutrition and high proinflammatory cytokine levels also induce the development of sarcopenia, which is characterized by reduced muscle mass and strength/function and is another common musculoskeletal comorbidity in patients with CLD [33]. Our previous studies of patients with cirrhosis revealed that the GNRI was a good predictor of sarcopenia, impaired physical performance, and prognosis [30, 45]. Given that the development and maintenance of the bones and muscles are inextricably linked, osteoporosis and sarcopenia frequently develop or progress concurrently, and the coexistence of these comorbidities is commonly referred to as osteosarcopenia [33]. Accordingly, patients with sarcopenia are more likely to develop osteoporosis and vice versa [46]. Osteoporosis and sarcopenia augment the risk of falls and fractures due to decreased muscle mass and strength and bone vulnerability [46, 47]. Collectively, osteoporosis and sarcopenia, which influence each other, are induced by malnutrition and chronic inflammation; thus, the GNRI may be able to simultaneously predict osteoporosis, sarcopenia, and fracture risk, as well as prognosis in patients with CLD.

This study had some limitations. First, inflammatory cytokines, which may affect the GNRI, were not measured. Second, patients with ascites (decompensated cirrhosis), who are more likely to be complicated by bone diseases, were excluded due to potential overestimation of BMI and GNRI. Third, the proportion or number of all-risk group patients was relatively small when compared to the no-risk group patients; thus, it is unclear whether osteoporosis prevalence and fracture risk increase as GNRI decreases (from low- to moderate- and major-risk groups). Finally, we did not compare GNRI to other nutritional assessment tools to determine whether it is better suited for predicting osteoporosis and fracture risk. In the future, prospective, large-scale, multicenter, and comparative studies are required to validate our findings and determine the optimal assessment method for malnutrition or nutritional status associated with osteoporosis and fragility-related fractures.

Conclusions

The GNRI was significantly associated with osteoporosis and FRAX-derived fracture risk in patients with CLD, suggesting that it could be a simple and useful indicator for managing bone diseases in such patients.

Abbreviations

AUC	Area under the curve
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
CLD	Chronic liver disease
eGFR	Estimated glomerular filtration rate
FRAX	Fracture risk assessment tool
GNRI	Geriatric nutritional risk index
HF	Hip fracture
IGF-1	Insulin-like growth factor 1

IL	Interleukin
M2BPGi	Mac-2 binding protein glycosylation isomer
MOF	Major osteoporotic fracture
OR	Odds ratio
PT	Prothrombin time
RA	Rheumatoid arthritis
TNF-α	Tumor necrosis factor-alpha
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions
C.S. and A.K. contributed to the conception and design of this study. H.K., C.S., T.O., T.K., K.U., M.N., and Y.T. acquired, analyzed, and interpreted the data. H.K., C.S., and A.T. drafted the manuscript. M.S. and A.T. interpreted the data and revised the manuscript. A.T. substantively revised and completed the manuscript. All authors read and approved the final version of the manuscript.

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Data availability
The datasets used and analyzed during this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study and its protocols conform to the 2013 Declaration of Helsinki and were approved by the ethics committees of Fuji City General Hospital (Approval no. 162) and the Jikei University School of Medicine (Approval no. 28–194). Written informed consent was obtained from all participants involved in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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