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# Prevalent osteoporosis and fracture risk in patients with hepatic cirrhosis: a systematic review and meta-analysis

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## Abstract

**Background** Hepatic liver cirrhosis can lead to significant systemic complications, including the deterioration of bone health. The resulting bone complications can contribute to a decreased quality of life and increased healthcare burden. This study aimed to systematically review and analyze the risk of osteoporosis, fracture, and changes in bone mineral density (BMD) among patients with hepatic cirrhosis compared to non-cirrhotic healthy controls.

**Methods** Adhering to PRISMA guidelines, studies were sourced from MEDLINE/PubMed, Scopus, Web of Science, and Embase up to July 2024, including observational studies that assessed osteoporosis, fracture, and BMD in cirrhotic versus non-cirrhotic patients. Meta-analyses were performed by calculating odds ratios (OR) and standardized mean differences (SMD) of outcomes. Sensitivity analyses and meta-regression were also conducted to explore the robustness and sources of heterogeneity.

**Results** The analysis included 21 studies with 76,521 cirrhotic and 695,330 control patients. Cirrhotic patients demonstrated significantly higher odds of osteoporosis (OR = 1.93 [1.84 to 2.03]). Fracture was notably elevated, with cirrhotic patients showing an OR of 2.30 [1.66 to 3.18]. Reductions in BMD were observed in both the lumbar spine (SMD = -0.57[-0.79 to -0.35]) and femoral neck (SMD = -0.41 [-0.71 to -0.12]). Sensitivity analyses confirmed these findings, and meta-regression highlighted that male prevalence impacted these associations in various ways.

**Conclusions** Patients with hepatic cirrhosis are at heightened risk for osteoporosis and fractures, underlining the need for proactive screening and preventive strategies. Integrating cirrhosis into current fracture-risk models could enhance the assessment and management of bone health in these patients.

**Keywords** Liver cirrhosis, Osteoporosis, Fracture, Bone mineral density (BMD), Systematic review, Meta-analysis

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## Introduction

Osteoporosis is characterized by bone tissue structural abnormalities and low bone mass (bone mineral density (BMD) T-score < − 2.5) leading to skeletal fragility and increased risk of fractures [1]. Osteoporosis can be primary, as seen in menopausal women and the elderly, or secondary, resulting from a variety of medical conditions or medications [2]. Cirrhosis is characterized by fibrosis, nodule formation, and impaired function due to chronic injury from causes like viral infections, alcohol, toxins, or autoimmune conditions with global estimates of 10·6 million cases of decompensated and 112 million cases of compensated cirrhosis in 2017 [3, 4].

Hepatic cirrhosis is one of the conditions associated with secondary osteoporosis [5]. According to previous research, osteoporosis affects 15–55.6% of patients with hepatic cirrhosis, making it a significant health concern for these individuals [5–7]. Osteoporosis can lead to an increase in incident fractures, hospitalizations, recovery time, morbidity and mortality, and healthcare costs [8–10]. These complications can cause a heavy burden on the quality of life of individuals with cirrhosis and the healthcare system which underscores the importance of understanding and addressing bone health in this population [9].

Although cirrhosis has previously been studied and recognized as a condition associated with osteoporosis, it has yet to be identified as a specific risk factor for fragility fractures and incorporated into fracture risk assessment tools and calculators such as FRAX, Garvan, and QFracture (chronic liver disease is a component of the QFracture score, not cirrhosis) [5, 6, 11–14]. These shortcomings, as well as the heterogeneous data available on the subject, necessitate a systematic review of the existing literature to determine the risk of osteoporosis and fragility fractures in patients with hepatic cirrhosis. Previous systematic reviews on this topic have primarily focused on the prevalence of osteoporosis in cirrhosis patients, whereas our goal is to determine whether there is a relationship between cirrhosis and osteoporosis and to what extent [5, 6].

## Materials and methods

The predetermined method used in this study is documented in the prospective register of systematic reviews (PROSPERO) (CRD42024532170). This meta-analysis was performed in accordance with the "preferred reporting items for systematic reviews and meta-analyses" (PRISMA) guidelines [15].

### Search strategy and screening

Two independent researchers (A.S. and A.G.R.) performed searches across the MEDLINE/PubMed, Scopus, Web of Science, and Embase databases. Additionally, a manual search was carried out using Google Scholar to locate relevant articles and publications related to the topic. The most recent citation search was completed in July 2024, just before the final analysis, using the following keyword terms: ("Liver cirrhosis"[Mesh] OR "Cirrhosis"[tiab] OR "Cirrhotic"[tiab] OR "Liver cirrhosis"[tiab] OR "Liver fibrosis"[tiab] OR "Hepatic fibrosis"[tiab] OR "Hepatic insufficiency"[tiab] OR "Liver failure"[tiab] OR "Hepatic cirrhosis"[tiab]) AND ("bone density"[MeSH] OR "fractures, bone"[MeSH] OR "osteoporosis"[MeSH] OR "osteoporosis"[Title/Abstract] OR "osteoporotic"[Title/Abstract] OR "osteoporoses"[Title/Abstract] OR "bone loss"[Title/Abstract] OR "fracture"[Title/Abstract] OR "bone demineralisation"[Title/Abstract] OR "bone demineralization"[Title/Abstract] OR "metabolic bone disease*"[Title/Abstract] OR "osteopenia"[Title/Abstract] OR "osteopenic"[Title/Abstract] OR "osteopaenia"[Title/Abstract] OR "osteopaenic"[Title/Abstract] OR "bone density"[Title/Abstract] OR "bone deterioration"[Title/Abstract] OR "bone mass density"[Title/Abstract] OR "bone mineral density"[Title/Abstract] OR "BMD"[Title/Abstract]). The studies were assessed using the online tool Rayyan (https://rayyan.ai/) for systematic reviews. After eliminating duplicates, two independent reviewers (Z.F.A. and F.M.E.) carefully evaluated the titles and abstracts of each study. The selected studies were subjected to detailed review, ensuring they met the inclusion and exclusion criteria during full-text screening. Any disagreements between the reviewers were resolved through consensus discussions, facilitated by the third author (A.H.H).

### Inclusion and exclusion criteria

For inclusion in the study, studies needed to meet PICOT criteria: (1) Participants: Adult patients; (2) Exposure: Liver cirrhosis; (3) Comparison: non-cirrhotic patients; (4) Outcome: osteoporosis diagnosis according to ICD-9 or ICD-10 (defined as the BMD less than 2 SD below the mean [16]), fracture, BMD parameters (T or Z score); (5) Types of studies: Observational studies. The following exclusion standards were set: (1) No non-cirrhotic control group; (2) Non-original studies such as letters to editors, technique articles, conference abstracts, pilot studies, meta-analyses, literature reviews and commentaries, animal research, and cadaver studies; (3) Other types of non-liver cirrhosis such as biliary cirrhosis; (4) Studies that do not report on osteoporosis, BMD, or fracture data.

### Data extraction and quality assessment

Two researchers (F.M.E. and A.G.R.) separately entered information into a pre-prepared Excel sheet following the full-text review. The data collected included osteoporosis

and fracture prevalence, mean bone mineral density (BMD), and demographic details such as publication year, study design, country, sample sizes for different groups, mean age, BMI, and percentage of male participants. Any discrepancies were resolved by a third author (A.H.H.). According to the included studies, osteoporosis was diagnosed when T-score was − 2.5 or lower, and osteopenia was defined by a T-score between − 1.0 and − 2.5. Some studies used Z-score, with a score below − 2.0 suggesting osteoporosis diagnosis.

Two authors independently assessed the quality of the studies using the Joanna Briggs Institute (JBI) critical appraisal checklists [17]. The JBI critical evaluation checklist consists of eleven components for cohort studies and eight for cross-sectional studies. The checklist assesses specific research topics in order to spot potential biases and offers simple binary choices. If the answer was yes, the question received a score of 1. Responses that were negative, ambiguous, or irrelevant were assigned a score of 0 [18].

### Data analyses

Data were processed using the "meta" package in R software. The odds ratio (OR) and corresponding 95% confidence intervals (CI) for categorical variables were calculated using the Mantel-Haenszel method. For continuous variables, Hedges' g standardized mean differences (SMD) and their 95% CIs were used as general indicators. Depending on the heterogeneity, either a fixed-effect or random-effects model was selected to combine study-specific effect estimates. Statistical heterogeneity was assessed using the Q-test and $I^2$ statistic. $I^2$ values ranging from 0 to 25% indicated low heterogeneity, 26–50% indicated moderate heterogeneity, and values above 50% reflected high heterogeneity. A fixed-effect model was applied if the P-value exceeded 0.1 and $I^2$ was below 50%; otherwise, a random-effects model was used [19]. Subgroup analysis was done based on the underlying etiology of cirrhosis (only viral vs. other types) as well as region and human development index (HDI) of the included studies. The HDI is a composite measure that assesses a country's average achievements in health, education, and income. It is categorized into four levels based on HDI scores: very high (≥ 0.800), high (0.700–0.799), medium (0.550–0.699), and low human development (< 0.550) [20, 21]. Sensitivity analysis was carried out by excluding one study at a time (backward elimination) to assess its effect on the overall results. Egger's test was used to assess potential publication bias [22]. A two-sided P-value below 0.05 was considered statistically significant for all analyses, except for heterogeneity. Meta-regression was performed to explore possible sources of heterogeneity, considering factors like population age, gender distribution, and study design.

## Results

### Study selection

A preliminary systematic search of databases identified 7,643 studies, with 3,638 duplicates removed. Out of 4,005 records, 3,921 studies that were not relevant were removed after title/abstract screening. A full assessment was conducted on 84 studies, with 21 meeting the inclusion criteria and being incorporated into the systematic review and meta-analysis [23–43] (Fig. 1).

### Baseline characteristics

The studies were conducted between 1996 [23] and 2023 [42, 43]. The study designs varied, including cross-sectional [23–32, 34, 37, 38, 41], cohort [33, 35, 36, 43], and case-control [39, 40, 42] Countries where studies were conducted include Egypt [28, 30], China [37, 40], Denmark [33, 36], Italy [25, 26], Taiwan [23, 35, 39], Spain [29, 31], Serbia [34], Brazil [27], Turkey [32], Greece [42], Japan [24], the UK [36], India [41], Austria [38], and Sweden [43]. Sample sizes across the studies was 76,521 in the cirrhotic group and 695,330 in the non-cirrhotic control group. The mean age of participants spanned from 34.8 ± 8.2 [32] to 74 [39]. The male percentage in the studies varied from 0% [26, 29] to 100% [34, 35, 41]. BMI data ranged from 22.4 ± 3.1 [37] to 31.7 ± 6.3 [29]. Table 1 summarizes additional data such as follow-up duration and cirrhosis diagnosis method and criteria.

### Risk of bias assessment

The quality assessment of the cross-sectional and case-control studies (Supplementary file 1: Table S1) revealed varying levels of methodological bias. Many studies [26, 31, 39, 42] demonstrated high quality, meeting all or nearly all criteria, particularly in areas such as the use of valid and reliable measurements and appropriate statistical analysis. However, several studies [23, 25, 27, 29, 30, 32, 34] were marked down for not detailing study subjects or settings and failing to identify or address confounding factors. Similarly, some studies [24, 28] had notable gaps in handling confounders and ensuring valid outcome measurements. For the cohort studies (Supplementary file 1: Table S2), the quality was generally higher, with studies meeting nearly all criteria. However, some studies [33, 35] did not fully address confounding factors, which lowered their methodological quality.

### Osteoporosis in cirrhotic patients vs. controls

Cirrhotic patients had higher odds of osteoporosis compared to healthy subjects (OR [95%CI] = 1.93 [1.84, 2.03]; I2 = 39%) (Fig. 2A). Subgroup analysis based on region and HDI revealed the same association between osteoporosis and cirrhosis except for medium HDI group [41] which showed no association (OR [95%CI] = 1.53 [0.54, 4.36]; I2 = N/A) (Fig. 2B). By excluding Gonzalez-Calvin

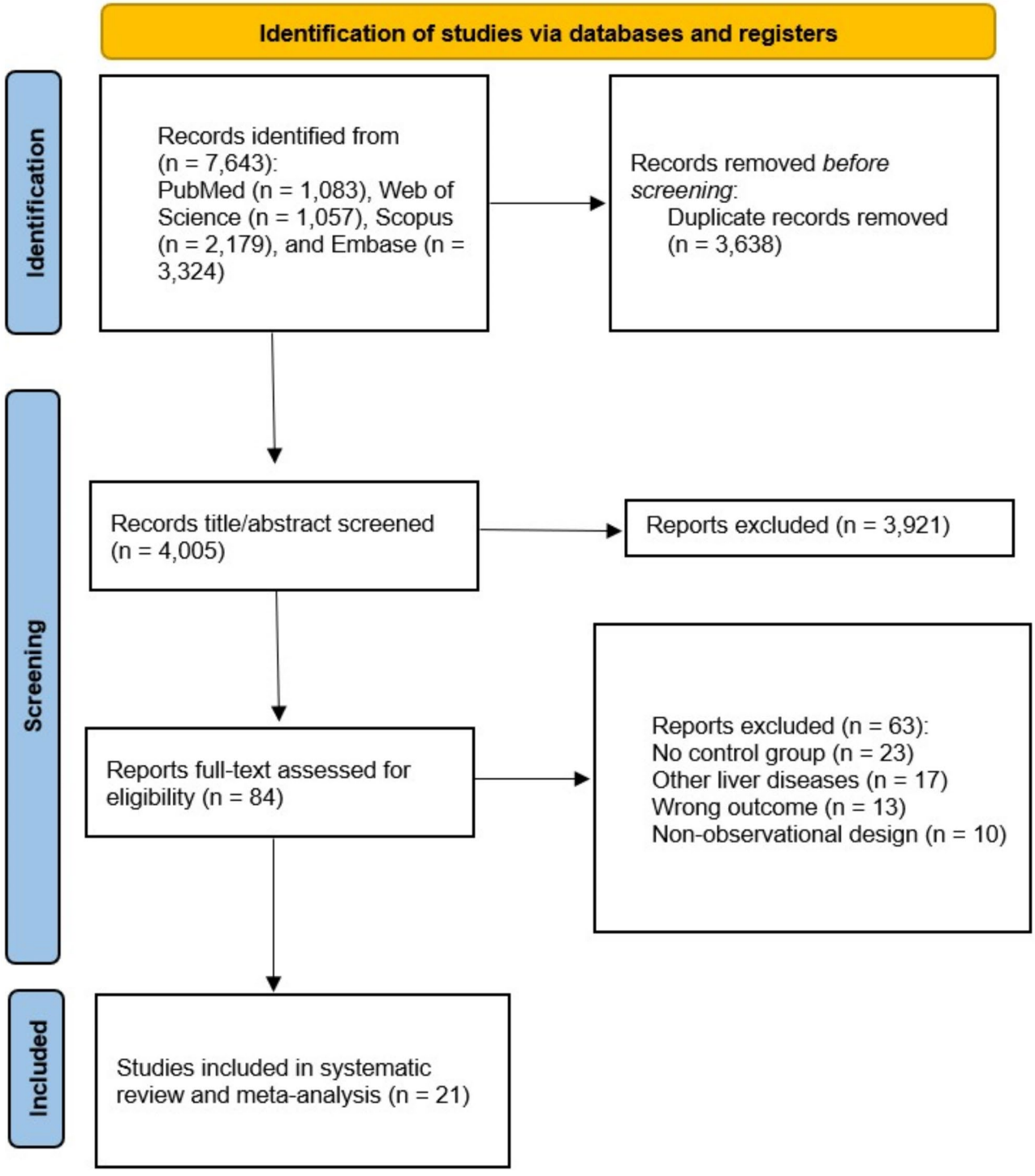


**Fig. 1** PRISMA flow diagram

**Table 1** Baseline characteristics of the studies

| Study | Study Design | Data Source | Country | Groups | Sample Size | Age, mean ± SD | Male, N (%) | BMI, mean ± SD | Follow-up years, mean ± SD | Child-Pugh Classification | | | Cirrhosis Diagnosis Criteria | Cirrhosis Diagnosis Method | Underlying Pathologies of Cirrhosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | A | B | C | | | |
| Ahmed, 2010 [30] | Cross-sectional | Patient Records | Egypt | Pre-menopausal females cirrhosis | 20 | 34.8 ± 8.5 | 0 (0) | 22.6 ± 2.2 | N/A | 0 | 10 | 10 | N/A | Clinical and sonographic | Post-hepatic |
| | | | | Control | 7 | | 0 (0) | 22.9 ± 2.6 | N/A | | | | | | |
| | | | | Post-menopausal females cirrhosis | 20 | 56.2 ± 4.0 | 0 (0) | 24.5 ± 1.3 | N/A | 0 | 14 | 6 | | | |
| | | | | Control | 7 | | 0 (0) | 24.5 ± 1.0 | N/A | | | | | | |
| | | | | Male cirrhosis | 20 | 52.8 ± 10.3 | 20 (100) | 23.6 ± 3.1 | N/A | 0 | 14 | 6 | | | |
| | | | | Control | 7 | | 7 (100) | 23.9 ± 1.3 | N/A | | | | | | |
| Bang, 2014 [33] | Retrospective Cohort | Danish nationwide registries | Denmark | Cirrhosis | 20,769 | 56.6 ± 11.0 | 13,396 (64.5) | N/A | 2.1 ± 3.0 | N/A | N/A | N/A | International Classification of Diseases, 10th edition | N/A | Alcohol |
| | | | | Control | 207,690 | 56.6 ± 11.0 | 133,960 (64.5) | N/A | | | | | | | |
| Casini, 2003 [26] | Cross-sectional | Patient Records | Italy | Late Post-menopausal cirrhosis | 27 | 62.1 ± 6.7 | 0 (0) | 25.0 ± 5.1 | 4.0 ± 0.8 | 27 | 0 | 0 | N/A | Clinical, biochemical and endoscopic | Viral (HBV, HCV), PBC |
| | | | | Late Post-menopausal healthy | 27 | 64.2 ± 5.2 | 0 (0) | 26.8 ± 1.9 | | | | | | | |
| | | | | Early Post-menopausal healthy | 27 | 51.7 ± 4.3 | 0 (0) | 24.9 ± 3.3 | | | | | | | |

**Table 1** (continued)

| Study | Study Design | Data Source | Country | Groups | Sample Size | Age, mean ± SD | Male, N (%) | BMI, mean ± SD | Follow-up years, mean ± SD | Child-Pugh Classification | | | Cirrhosis Diagnosis Criteria | Cirrhosis Diagnosis Method | Underlying Pathologies of Cirrhosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | A | B | C | | | |
| Chang, 2020 [39] | Case-control | National Health Insurance Research Database | Taiwan | Cirrhosis | 4,048 | 71.2 | 2054 (50.7) | N/A | N/A | N/A | N/A | N/A | Based on ICD-9-CM codes 571.2, 571.5, and 571.6 | N/A | Alcohol, PBS |
| | | | | No cirrhosis | 113,081 | 74 | 47,187 (41.7) | N/A | N/A | | | | | | |
| Chen, 1996 [23] | Cross-sectional | Patient Records | Taiwan | Cirrhosis | 74 | 64.1 ± 9.9 | 74 (100) | N/A | N/A | 30 | 21 | 23 | N/A | Clinical, biochemical, and sonographic | Alcohol, viral (HBV, HCV), drug, cryptogenic |
| | | | | No cirrhosis | 16 | 63.6 ± 9.0 | 16 (100) | N/A | N/A | | | | | | |
| Chen, 2017 [35] | Cohort | Taiwan's National Health Insurance Programme | Taiwan | Cirrhosis | 3941 | 54.1 ± 14.1 | 2696 (68.4) | N/A | 8 | 0 | 0 | 0 | N/A | N/A | N/A |
| | | | | No cirrhosis | 15,764 | 53.9 ± 14.2 | 10,784(68.4) | N/A | | | | | | | |
| Corazza, 2000 [25] | Cross-sectional | Patient Records | Italy | Cirrhosis | 31 | 57.2 ± 9.3 | 22 (71.0) | N/A | N/A | 8 | 11 | 12 | N/A | N/A | Viral (HBV, HCV) |
| | | | | No cirrhosis | 37 | 57.3 ± 9.2 | 25 (67.6) | N/A | N/A | | | | | | |
| Culafic, 2014 [34] | Cross-sectional | Patient records | Serbia | Cirrhosis | 33 | 56.2 ± 12.2 | 33(100) | 26.7 ± 4.0 | N/A | 12 | 10 | 11 | Presence of at least two of the findings of nodular irregular surfaces, distorted vascular pattern, dilated splenic and portal veins, or ascites, hypertensive portal gastropathy, esophageal or gastric varices | Medical history, laboratory, clinical, sonography, upper endoscopy, and liver biopsy | Alcohol |
| | | | | No cirrhosis | 36 | 54.9 ± 13.0 | 36(100) | 28.3 ± 4.4 | N/A | | | | | Histological | |

**Table 1** (continued)

| Study | Study Design | Data Source | Country | Groups | Sample Size | Age, mean ± SD | Male, N (%) | BMI, mean ± SD | Follow-up years, mean ± SD | Child-Pugh Classification | | | Cirrhosis Diagnosis Criteria | Cirrhosis Diagnosis Method | Underlying Pathologies of Cirrhosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | A | B | C | | | |
| Diez-Ruiz, 2010 [31] | Cross-sectional | Patient records | Spain | Cirrhosis | 33 | 53.1 ± 9.6 | 33(100) | N/A | N/A | 10 | 13 | 10 | N/A | Clinical, imaging, and liver biopsy | Alcohol |
| | | | | No cirrhosis | 24 | 52.1 ± 11.7 | N/A | N/A | N/A | | | | | | |
| Ezzat, 2007 [28] | Cross-sectional | N/A | Egypt | Cirrhosis | 25 | N/A | 16(64) | N/A | N/A | N/A | N/A | N/A | Presence of ascitis, lower limb oedema, hepatic encephalopathy, shrunken liver and/or portal hypertension and/or ascitis | Clinical, laboratory, and sonography | HCV |
| | | | | No cirrhosis | 33 | N/A | 21 (64) | N/A | N/A | | | | | | |
| Figueiredo, 2003 [27] | Cross-sectional | Patient Records | Brazil | Cirrhosis | 89 | 52 ± 11 | 55(62) | N/A | N/A | 32 | 34 | 23 | Signs of portal hypertension and hepatic insufficiency | Laparoscopy and histological | Non-cholestatic |
| | | | | No cirrhosis | 20 | 45 ± 15 | 8(40) | 25.4 ± 4.6 | N/A | | | | | | |
| Gonzalez-Calvin, 2009 [46] | Cross-sectional | Patient Records | Spain | Cirrhosis | 84 | 65.1 ± 6.3 | 0 (0) | 30.9 ± 5.5 | N/A | 54 | 30 | | Physical signs of chronic liver disease, hypoalbuminemia, reduced prothrombin activity, signs of liver cirrhosis on ultrasound examination, and esophageal varices on endoscopy | Liver biopsy, clinical, and laboratory | Viral (HBV, HCV) |
| | | | | No cirrhosis | 96 | 63.8 ± 6.0 | 0 (0) | 31.7 ± 6.3 | N/A | | | | | | |

**Table 1** (continued)

| Study | Study Design | Data Source | Country | Groups | Sample Size | Age, mean ± SD | Male, N (%) | BMI, mean ± SD | Follow-up years, mean ± SD | Child-Pugh Classification | | | Cirrhosis Diagnosis Criteria | Cirrhosis Diagnosis Method | Underlying Pathologies of Cirrhosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | A | B | C | | | |
| Goral, 2010 [32] | Cross-sectional | Patient Records | Turkey | Cirrhosis | 85 | 44.8 ± 12.9 | 55(64.7) | 25.5 ± 4.3 | N/A | 14 | 17 | 24 | N/A | Biochemical, serological, sonography, upper endoscopy | Viral (HBV, HCV), cryptogenic, PBC, cardiac, storage diseases |
| | | | | No cirrhosis | 30 | 34.8 ± 8.2 | 15(50) | 25.5 ± 3.7 | N/A | | | | | | |
| Katsaounis, 2022 [42] | Case-control | Patient Records | Greece | Cirrhosis | 74 | 59.2 ± 9.4 | 50 (67) | 26.3 | N/A | 34 | 17 | 23 | N/A | Laboratory | Alcohol, viral (HBV, HCV), autoimmune, NAFLD, storage diseases |
| | | | | No cirrhosis | 25 | 56.6 ± 11.5 | 17 (68) | 27.7 | N/A | | | | | | |
| Masaki, 1998 [24] | Cross-sectional | Patient Records | Japan | Cirrhosis | 184 | N/A | 98(53.2) | N/A | N/A | N/A | N/A | N/A | | Histological (laparoscopy and biopsy) | Viral (HBV, HCV) |
| | | | | No cirrhosis | 905 | N/A | 283(31.3) | N/A | N/A | | | | | | |
| Otete, 2018 [36] | Cohort | Clinical Practice Research Datalink and Hospital Episodes Statistics database | UK | Cirrhosis | 3706 | 55.6 ± 2.4 | 2,520 (68.0) | N/A | | N/A | N/A | N/A | ICD-10 code | N/A | Alcohol, viral (HBV, HCV), autoimmune, metabolic |
| | | | | No cirrhosis | 36,854 | 55.4 ± 12.6 | 25,074 (68.0) | N/A | | | | | | | |
| | | The Danish National Patient Registry and the Danish civil registration system | **Denmark** | Cirrhosis | 17,779 | 57.0 ± 10.4 | 11,687 (66.8) | N/A | 17 | N/A | N/A | N/A | ICD-10 code | N/A | Alcohol, viral (HBV, HCV), autoimmune, metabolic |
| | | | | No cirrhosis | 80,815 | 57.0 ± 10.4 | 52,633 (65.1) | N/A | 17 | | | | | | |

**Table 1** (continued)

| Study | Study Design | Data Source | Country | Groups | Sample Size | Age, mean ± SD | Male, N (%) | BMI, mean ± SD | Follow-up years, mean ± SD | Child-Pugh Classification | | | Cirrhosis Diagnosis Criteria | Cirrhosis Diagnosis Method | Underlying Pathologies of Cirrhosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | A | B | C | | | |
| Thakur, 2022 [41] | Cross-sectional | Patient Records | India | Cryptogenic cirrhosis | 30 | 39.3 ± 9.2 | 30(100) | 23.1 ± 3.8 | N/A | 30 | 0 | 0 | Coarse-pattern, irregular liver surface, clear-cut evidence of portal hypertension such as splenomegaly and esophagogastric varices) | Imaging/endoscopic and/or histopathological | Alcohol, drugs, viral (HBV, HCV), autoimmune, PBC, PSC, storage diseases |
| | | | | Hepatitis B cirrhosis | 30 | 39.8 ± 8.3 | 30(100) | 24.8 ± 3.9 | N/A | N/A | N/A | N/A | | | HBV |
| | | | | No cirrhosis | 30 | 39.3 ± 3.5 | 30(100) | 23.9 ± 1.5 | N/A | | | | | | |
| Wakolbinger, 2019 [38] | Cross-sectional | Patient Records | Austria | Cirrhosis | 32 | 62.4 ± 8.5 | 20(62.5) | 26.9 ± 5.8 | N/A | N/A | N/A | N/A | N/A | Clinical, medical history, imaging (sonography, CT scan, or magnetic resonance imaging), and laboratory | Alcohol, viral (HBV, HCV), autoimmune, NAFLD, storage diseases |
| | | | | No cirrhosis | 32 | 60.3 ± 10.1 | 20(62.5) | 27.2 ± 4.4 | N/A | | | | | | |
| Wester, 2023 [43] | Cohort | The Swedish National Patient Registry | Sweden | Cirrhosis | 25,090 | 59.7 ± 11.1 | 19,016 (75.8) | N/A | 2.1 ± 3.6 | N/A | N/A | N/A | N/A | N/A | Alcohol |
| | | | | No cirrhosis | 239,458 | 59.7 ± 11.1 | 181,455 (75.8) | N/A | 12.8 ± 11.9 | | | | | | |
| Zhang, 2020 [40] | Case-control | Patient Records | China | Cirrhosis | 80 | 51.7 ± 9.6 | 44 (55.0) | 23.9 ± 4.2 | N/A | 57 | 16 | 7 | Guidelines of the American Association for the Study of Liver Diseases | Laboratory, histology, or imaging | HBV |
| | | | | No cirrhosis | 80 | 54.7 ± 10.8 | 40 (50.0) | 24.5 ± 3.1 | N/A | | | | | | |

**Table 1** (continued)

| Study | Study Design | Data Source | Country | Groups | Sample Size | Age, mean ± SD | Male, N (%) | BMI, mean ± SD | Follow-up years, mean ± SD | Child-Pugh Classification | | | Cirrhosis Diagnosis Criteria | Cirrhosis Diagnosis Method | Underlying Pathologies of Cirrhosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | A | B | C | | | |
| Zheng, 2018 [37] | Cross-sectional | Patient Records | China | Cirrhosis | 217 | 57.2 ± 10.3 | 161 (74.2) | 22.4 ± 3.1 | N/A | 217 | 0 | 0 | N/A | Liver histopathologic, computed tomography, or magnetic resonance imaging | Alcohol, viral (HBV, HCV) |
| | | | | No cirrhosis | 229 | 56.7 ± 9.4 | 158 (69.0) | 22.7 ± 3.8 | N/A | | | | | | |

*Abbreviations* CT, Computed Tomography; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; ICD-10, International Classification of Diseases, 10th Edition; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; MRI, Magnetic Resonance Imaging; NAFLD, Non-alcoholic Fatty Liver Disease; N/A, Not Applicable; PBC, Primary Biliary Cirrhosis; PSC, Primary Sclerosing Cholangitis; SD, Standard Deviation; UK, United Kingdom; NASH, Nonalcoholic Steatohepatitis

et al. [29], the association between osteoporosis and cirrhosis remained, with heterogeneity reduced (OR [95%CI] = 1.94 [1.85, 2.04]; I2 = 26%) (Supplementary file 1: Figure S1). Meta-regression revealed that studies with a higher prevalence of males ($p = 0.03$) (Supplementary file 1: Figure S2) had reduced odds of osteoporosis in cirrhotic patients compared to controls. Study design and population mean age were found not be possible sources of heterogeneity ($p > 0.05$).

#### Fractures in cirrhotic patients vs. controls

Patients exhibited a notably increased prevalence of fractures in contrast to the control group (OR [95%CI] = 2.30 [1.66, 3.18]; I2 = 98%) (Fig. 3). By omitting Chen et al. [35], there was a slight reduction observed in the meta-analysis, with the association remaining intact (OR [95%CI] = 2.62 [2.02, 3.40]; I2 = 95%) (Supplementary file 1: Figure S3). Study design, mean age, and male prevalence across the included studies was found not be a possible source of heterogeneity ($p > 0.05$).

#### Bone mineral density in cirrhotic patients vs. controls

Cirrhotic patients exhibited a notable decrease in BMD in the lumbar region in comparison to the control group (SMD [95%CI] = -0.57 [-0.79, -0.35]; I2 = 66%) (Fig. 4A). Subgroup analysis based on underlying etiology of cirrhosis revealed the same association in viral only (SMD [95%CI] = -0.49 [-0.76, -0.22]; I2 = 63.4%) and other etiologies (SMD [95%CI] = -0.67 [-1.03, -0.32]; I2 = 72.5%) subgroups (Fig. 4B). Excluding Zheng et al. [37] from the lumbar BMD sensitivity analysis resulted in a reduction in heterogeneity but did not change overall outcome (SMD [95%CI] = -0.63 [-0.86, -0.41]; I2 = 53%) (Supplementary file 1: Figure S4). The study design, average age, and proportion of males in the studies were not identified as potential causes of variation ($p > 0.05$).

The femoral neck BMD also showed a significant decrease (SMD [95%CI] = -0.41 [-0.71, -0.12]; I2 = 72%) in the cirrhotic group (Fig. 4C). Subgroup analysis based on underlying etiology of cirrhosis revealed that in the viral only subgroup no statistically significant difference in femoral neck BMD was observed between cirrhotic and non-cirrhotic patients (SMD [95%CI] = -0.13 [-0.55, 0.30]; I2 = 74.5%), a finding in contrast with the other etiologies subgroup (SMD [95%CI] = -0.57 [-0.88, -0.26]; I2 = 56.7%) (Fig. 4D). Excluding Gonzalez-Calvin et al. [29] did not change the correlation between femoral neck BMD and cirrhosis (SMD [95%CI] = -0.49 [-0.71, -0.28]; I2 = 46%) (Supplementary file 1: Figure S5). Meta-regression analysis showed that studies with a larger prevalence of male participants had increased association between femoral neck BMD in cirrhotic patients when compared to controls ($p = 0.04$) (Supplementary file 1: Figure S6).

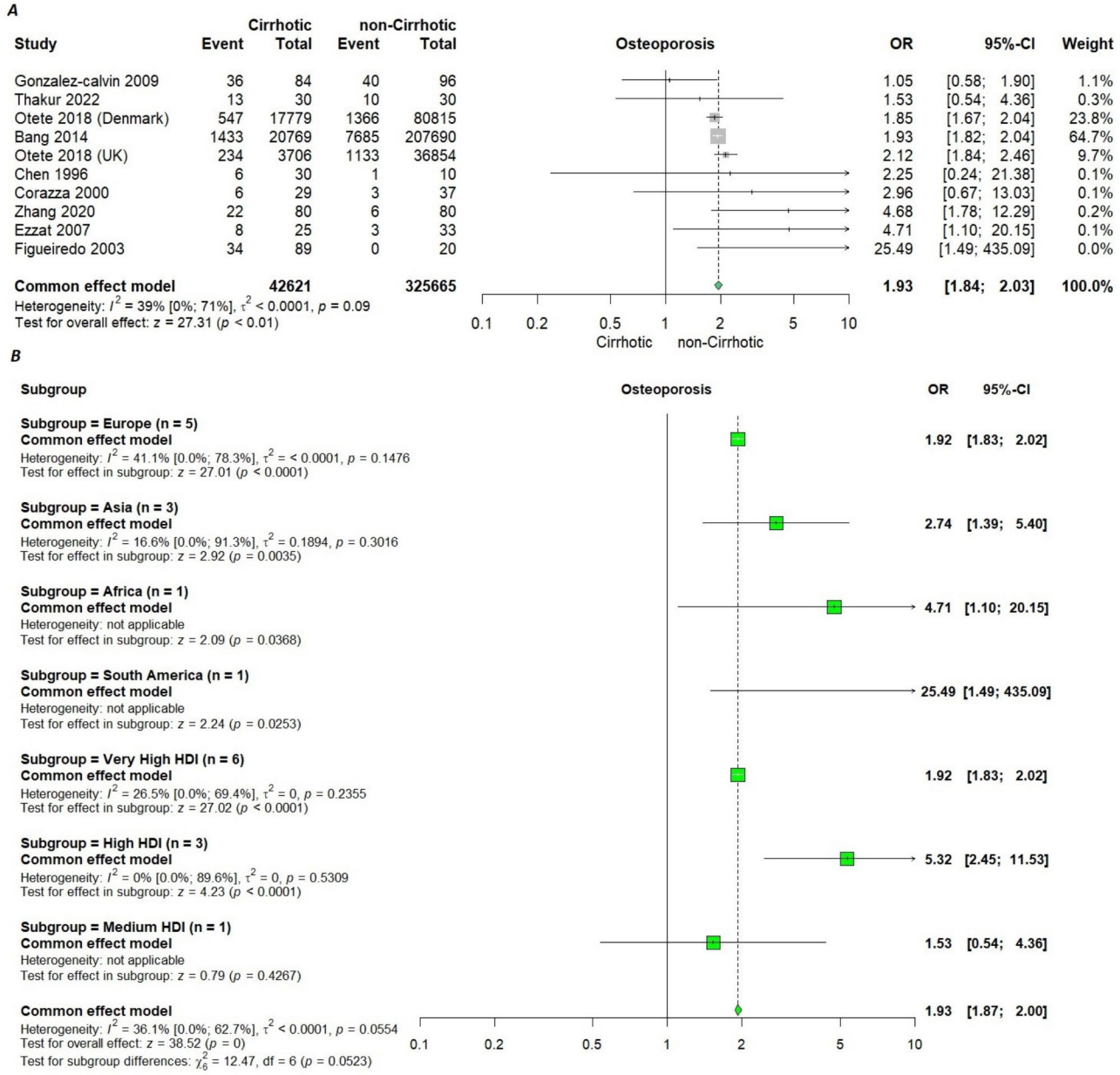


**Fig. 2** **(A)** Forest plot of osteoporosis in cirrhotic vs. non-cirrhotic patients; **(B)** Subgroup analysis of osteoporosis based on region and HDI in cirrhotic vs. non-cirrhotic patients

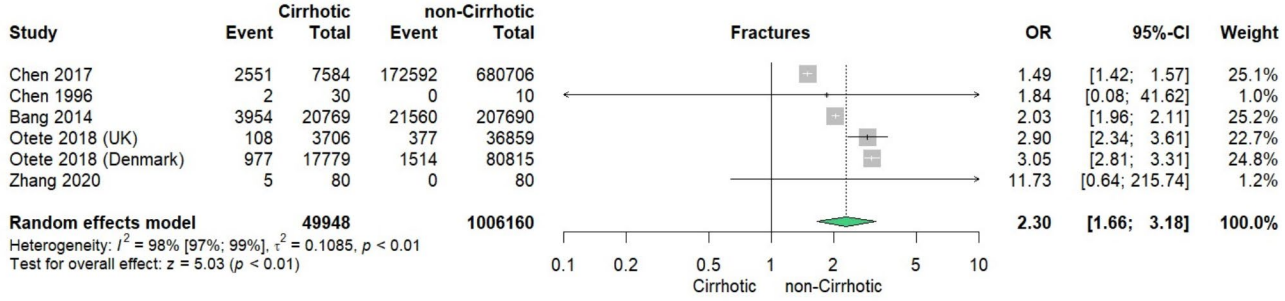


**Fig. 3** Forest plot of fractures in cirrhotic vs. non-cirrhotic patients

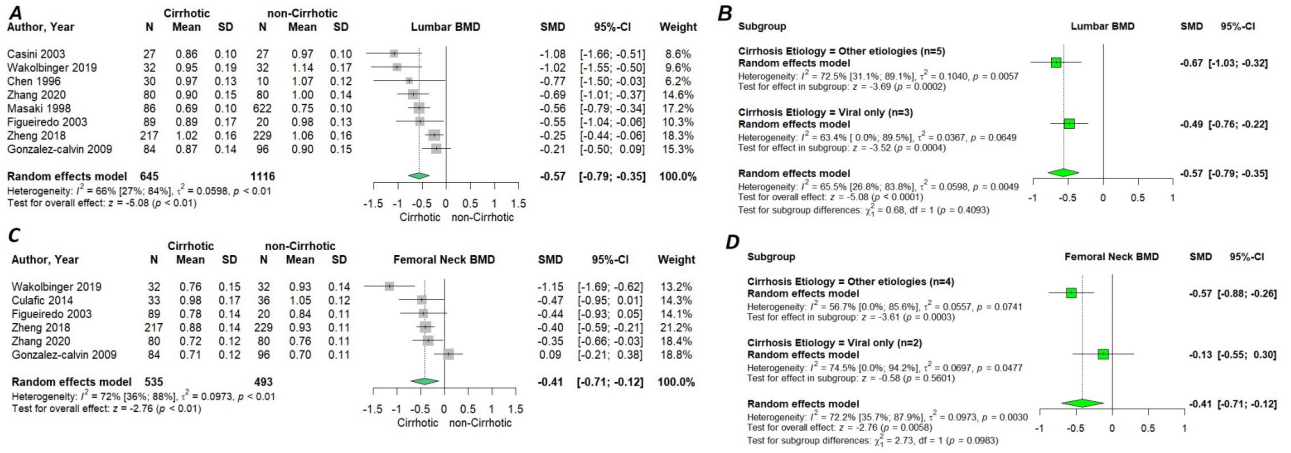


**Fig. 4** **(A)** Forest plot of lumbar BMD in cirrhotic vs. non-cirrhotic patients; **(B)** Subgroup analysis of lumbar BMD based on cirrhosis underlying etiology in cirrhotic vs. non-cirrhotic patients; **(C)** Forest plot of femoral neck BMD in cirrhotic vs. non-cirrhotic patients; **(D)** Subgroup analysis of femoral neck BMD based on cirrhosis underlying etiology in cirrhotic vs. non-cirrhotic patients

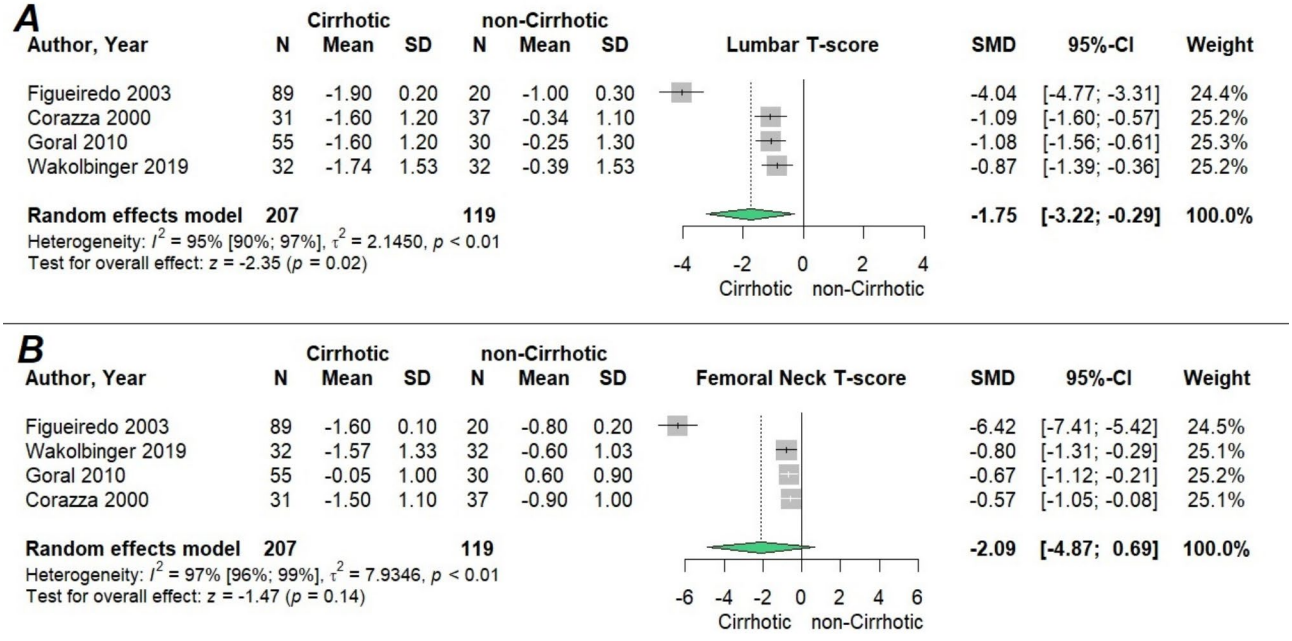


**Fig. 5** **(A)** Forest plot of lumbar T-score in cirrhotic vs. non-cirrhotic patients; **(B)** Forest plot of femoral neck T-score in cirrhotic vs. non-cirrhotic patients

Study design and mean age had no effect according to meta regression ($p > 0.05$).

Patients had a significantly lower lumbar T-score compared to controls (SMD [95%CI] = -1.75 [-3.22, -0.29]; I2 = 95%) (Fig. 5A). The strongest reduction in the heterogeneity was seen when Figueiredo et al. [27] was eliminated, with the association still present (SMD [95%CI] = -1.02 [-1.31, -0.73]; I2 = 0%) (Supplementary file 1: Figure S7). Studies with a higher proportion of male participants demonstrated a lower correlation between lumbar T-score in cirrhotic patients and controls ($p = 0.03$) (Supplementary file 1: Figure S8). Study design and age were computed to have no significant effect ($p > 0.05$).

The femoral neck T-score (SMD [95%CI] = -2.09 [-4.87, 0.69]; I2 = 97%) was determined to be statistically similar in patients and healthy subjects (Fig. 5B). Excluding Figueiredo et al. [27] revealed an inverse relationship between femoral neck T-score and cirrhosis (SMD [95%CI] = -0.67 [-0.95, -0.39]; I2 = 0%) (Supplementary file 1: Figure S9). Meta-regression showed that research with a larger percentage of males exhibited lower association of femoral neck T-score in cirrhotic vs. non-cirrhotic patients ($p = 0.02$) (Supplementary file 1: Figure S10). There was no significant impact found on the study design and age ($p > 0.05$).

The cirrhotic group had a significantly lower lumbar Z-score than the control group (SMD [95%CI] = -1.04 [-1.97, -0.11]; I2 = 94%) (Fig. 6A). Omission of the study by Figueiredo et al. [27] resulted in a decrease in heterogeneity (SMD [95%CI] = -0.57 [-0.96, -0.19]; I2 = 75%) based on sensitivity analysis (Supplementary file 1: Figure S11). The potential causes of heterogeneity, namely study design, average age, and proportion of males, were not specified ($p > 0.05$).

The Z-score at the femoral neck level was similar in both cirrhotic and non-cirrhotic individuals (SMD [95%CI] = -8.97 [-25.65, 7.71]; I2 = 98%) (Fig. 6B). An inverse association between cirrhosis and femoral neck Z-score was discovered when Figueiredo et al. [27] was not included in the sensitivity analysis (SMD [95%CI] = -0.46 [-0.90, -0.03]; I2 = 79%) (Supplementary file 1: Figure S12). The study's design, mean age, and male distribution were not pinpointed as possible sources of heterogeneity ($p > 0.05$).

### Qualitative synthesis

The qualitative synthesis of bone health and fracture prevalence in cirrhotic versus control populations across several studies is summarized in Table 2. In the Ahmed et al.'s study [30], pre-menopausal cirrhotic patients had a significantly lower mean calcaneal T-score (-1.5 ± 0.2) compared to controls (-0.3 ± 0.2) ($p < 0.001$). Similarly, post-menopausal cirrhotic women had a reduced mean calcaneal T-score (-2.7 ± 0.3) compared to controls (-1.3 ± 0.2) ($p < 0.05$). In males, the mean calcaneal T-score was also notably lower in cirrhotic patients (-1.8 ± 0.3) compared to controls (0.5 ± 0.3) ($p < 0.001$). In Katsaounis et al. [42], both lumbar spine and femoral bone T-scores were lower in cirrhotic patients (median = -1.46 and – 1.37, respectively) compared to controls (median = -0.40 and – 0.67), with a significant correlation in femoral bone T-scores ($r = 0.31$; $p = 0.03$) but not lumbar spine T-scores ($r = 0.24$; $p = 0.08$).

Wakolbinger et al. [38] found significantly lower total hip BMD, total body BMD, and radius BMD in cirrhotic patients compared to controls (all $p < 0.05$). The total hip T-score and Z-score were also significantly lower ($p = 0.005$ and $p = 0.012$, respectively). Also, Zheng et al. [37] observed a significant reduction in hip BMD among cirrhotic patients (0.88 ± 0.14 g/cm²) compared to controls (0.93 ± 0.11 g/cm²) ($p < 0.001$). Conversely, Culafic et al. [34] observed no significant difference in total hip BMD between cirrhotic patients (1.02 ± 0.02 g/cm²) and controls (1.02 ± 0.02 g/cm²).

Casini et al. [26] found that total BMD was lower in cirrhotic patients (1.01 ± 0.02 g/cm²) compared to controls (1.06 ± 0.01 g/cm²) ($p < 0.05$). Similarly, Zhang et al. [40] reported lower BMD in cirrhotic patients for Ward's triangle (0.65 ± 0.10 g/cm² vs. 0.69 ± 0.09 g/cm², $p = 0.006$) and total hip BMD (0.89 ± 0.13 g/cm² vs. 0.93 ± 0.11 g/

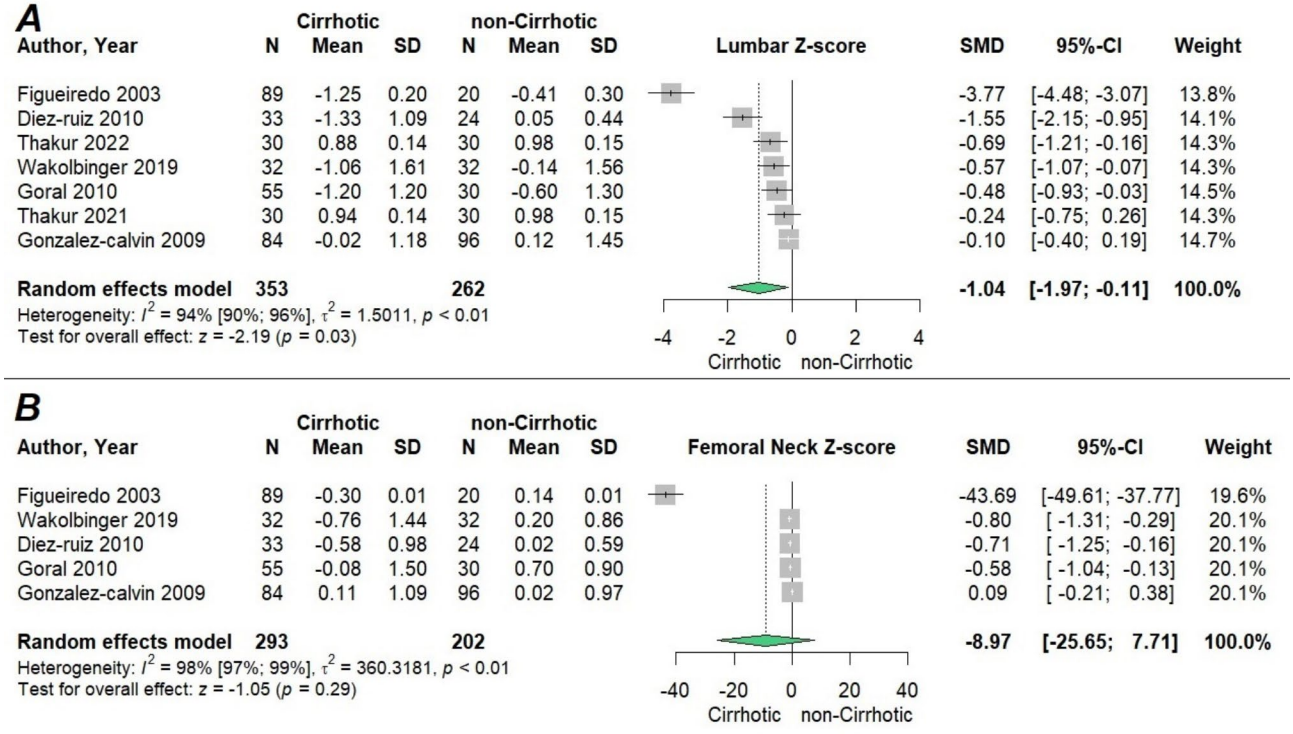


**Fig. 6** **(A)** Forest plot of lumbar Z-score in cirrhotic vs. non-cirrhotic patients; **(B)** Forest plot of femoral neck Z-score in cirrhotic vs. non-cirrhotic patients

**Table 2** Summarized qualitative data synthesis

| Study | Cirrhotic | Control | Association | *P*-value |
|---|---|---|---|---|
| Ahmed, 2010 [30] (Pre-menopausal) | Calcaneal T-score, mean ± SE = -1.5 ± 0.2 | Calcaneal T-score, mean ± SE = -0.3 ± 0.2 | N/A | < 0.001 |
| Ahmed, 2010 [30] (Post-menopausal) | Calcaneal T-score, mean ± SE = -2.7 ± 0.3 | Calcaneal T-score, mean ± SE = -1.3 ± 0.2 | N/A | < 0.05 |
| Ahmed, 2010 [30] (Male) | Calcaneal T-score, mean ± SE = -1.8 ± 0.3 | Calcaneal T-score, mean ± SE = 0.5 ± 0.3 | N/A | < 0.001 |
| Chang, 2020 [39] | Annual incidence of hip fractures = 46–54 per 10,000 person-years | Annual incidence of hip fractures = 7–7.5 per 10,000 person-years | Incidence rate ratio = 6.95 [95% CI = 6.74–7.18] | N/A |
| Culafic, 2014 [34] | Total hip BMD (g/cm2), mean ± SE = 1.02 ± 0.02 | Total hip BMD (g/cm2), mean ± SE = 1.02 ± 0.02 | N/A | N/A |
| Diez-ruiz, 2010 [31] | Osteoporosis = 13/33 | N/A | N/A | N/A |
| Casini, 2003 [26] | Head BMD (g/cm2), mean ± SE = 2.16 ± 0.04<br>Arm BMD (g/cm2), mean ± SE = 0.77 ± 0.02<br>Legs BMD (g/cm2), mean ± SE = 1.02 ± 0.02<br>Trunk BMD (g/cm2), mean ± SE = 0.76 ± 0.02<br>Ribs BMD (g/cm2), mean ± SE = 0.57 ± 0.01<br>Pelvis BMD (g/cm2), mean ± SE = 0.93 ± 0.03<br>Total BMD (g/cm2), mean ± SE = 1.01 ± 0.02 | Head BMD (g/cm2), mean ± SE = 2.12 ± 0.04<br>Arm BMD (g/cm2), mean ± SE = 0.81 ± 0.01<br>Legs BMD (g/cm2), mean ± SE = 1.10 ± 0.02<br>Trunk BMD (g/cm2), mean ± SE = 0.84 ± 0.02<br>Ribs BMD (g/cm2), mean ± SE = 0.62 ± 0.01<br>Pelvis BMD (g/cm2), mean ± SE = 1.03 ± 0.02<br>Total BMD (g/cm2), mean ± SE = 1.06 ± 0.01 | N/A | < 0.05 |
| Katsaounis, 2022 [42] | Lumbar spine T-score, median = -1.46<br>Femoral bone T-score, median = -1.37 | Lumbar spine T-score, median = -0.40<br>Femoral bone T-score, median = -0.67 | Lumbar Spearman's rho = 0.24<br>Femoral Spearman's rho = 0.31 | Lumbar = 0.08<br>Femoral = 0.03 |
| Wakolbinger, 2019 [38] | Total hip BMD (g/cm2), median (Q1-Q3) = 0.91 (0.80–1.03)<br>Total hip T-score median (Q1-Q3) = − 1.1 (− 2.1 to − 0.28)<br>Total hip Z-score median (Q1-Q3) = − 0.4 (− 1.38–0.33)<br>Total body BMD (g/cm2), median (Q1-Q3) = 1.12 (0.95–1.19)<br>Radius BMD (g/cm2), median (Q1-Q3) = 0.61 (0.55–0.70)<br>Calcaneus BMD (g/cm2), median (Q1-Q3) = 0.38 (0.30–0.41) | Total hip BMD (g/cm2), median (Q1-Q3) = 1.02 (0.96–1.20)<br>Total hip T-score median (Q1-Q3) = − 0.1 (− 0.73–0.4)<br>Total hip Z-score median (Q1-Q3) = 0.45 (− 0.1–0.8)<br>Total body BMD (g/cm2), median (Q1-Q3) = 1.22 (1.13–1.30)<br>Radius BMD (g/cm2), median (Q1-Q3) = 0.74 (0.64–0.81)<br>Calcaneus BMD (g/cm2), median (Q1-Q3) = 0.51 (0.47–0.53) | N/A | Total hip BMD = 0.006<br>Total hip T-score = 0.005<br>Total hip Z-score = 0.012<br>Total body BMD = 0.003<br>Radius BMD = 0.001<br>Calcaneus BMD = 0.003 |
| Wester, 2023 [43] | Any fracture = 3659 (14.6%)<br>Incidence per 1000 person-years [95%CI] = 38.7 (37.4–39.9) | Any fracture = 44,976 (18.8%)<br>Incidence per 1000 person-years [95%CI] = 13.3 (13.2–13.5) | aHR [95%CI] = 3.8 [3.6–3.9] | < 0.001 |
| Zhang, 2020 [40] | Ward's triangle BMD (g/cm2), mean ± SD = 0.65 ± 0.10<br>Trochanter BMD (g/cm2), mean ± SD = 1.08 ± 0.16<br>Total hip (g/cm2), mean ± SD = 0.89 ± 0.13 | Ward's triangle BMD (g/cm2), mean ± SD = 0.69 ± 0.09<br>Trochanter BMD (g/cm2), mean ± SD = 1.13 ± 0.14<br>Total hip (g/cm2), mean ± SD = 0.93 ± 0.11 | N/A | Ward's triangle BMD = 0.006<br>Trochanter BMD = 0.040<br>Total hip = 0.015 |
| Zheng, 2018 [37] | Hip BMD (g/cm2), mean ± SD = 0.88 ± 0.14 | Hip BMD (g/cm2), mean ± SD = 0.93 ± 0.11 | N/A | < 0.001 |

*Abbreviations* aHR, Adjusted Hazard Ratio; BMD, Bone Mineral Density; CI, Confidence Interval; N/A, Not Applicable; Q1-Q3, Quartile 1 to Quartile 3; SD, Standard Deviation; SE, Standard Error

$cm^2$, $p = 0.015$), though no significant difference was observed for trochanter BMD.

Wester et al. [43] reported a significantly higher incidence of fractures in cirrhotic patients (14.6%) compared to controls (18.8%), with an adjusted hazard ratio (aHR) of 3.8 [95% CI: 3.6–3.9] ($p < 0.001$). Chang et al. [39] also reported a higher annual incidence of hip fractures in cirrhotic patients (46–54 per 10,000 person-years) compared to controls (7–7.5 per 10,000 person-years), with an incidence rate ratio of 6.95 [95% CI: 6.74–7.18].

### Publication bias

Egger's test and funnel plot (Supplementary file 1: Figure S13) was computed on the meta-analysis with the most studies, namely osteoporosis prevalence in cirrhotic vs. non-cirrhotic, and hence no publication bias was observed (P-value = 0.985).

## Discussion

In this systematic review and meta-analysis, we comprehensively evaluated the relationship between hepatic cirrhosis and the prevalence of osteoporosis and fracture risk. Our results show that patients with cirrhosis are 1.93 times more likely to develop osteoporosis and have a 2.3 times higher risk of fractures compared to non-cirrhotic controls. Our results are consistent with a previous systematic review and meta-analysis including 8 studies up to 2017 that showed liver cirrhosis is associated with an increased risk of fracture with an OR of 1.94 (95% CI: 1.59–2.37) [14]. Another meta-analysis found that cirrhotic patients have a 2.52 times greater risk of osteoporosis (95% CI: 1.11–5.69), which is in line with our findings [5]. A more recent meta-analysis also showed an association between cirrhosis and an increased prevalence of osteoporosis, with a pooled prevalence of 15% [6].

Several factors may contribute to the increased risk of osteoporosis in cirrhosis patients which generally consist of a combination of increased osteoclastic and decreased osteoblastic activity leading to an imbalance in remodeling mechanisms [44]. The mechanisms by which this happens are not yet completely understood but may result from decreased vitamin D, vitamin K, and calcium levels, impaired growth hormone and insulin-like growth factor-1 (IGF-1) secretion, increased inflammatory mediators TNF-alpha and IL-6, hyperbilirubinemia, limited physical activity, malnutrition, and alcohol consumption [6, 31, 45, 46]. Previous meta-analyses point to significantly lower levels of 25-hydroxyvitamin D and IGF-1 in cirrhosis patients [5, 6]. IGF-1 may protect against BMD loss and fracture by promoting osteoblast proliferation and function, as well as bone formation [47, 48]. Another proposed mechanism for IGF-1 is maintaining optimal levels of bone matrix and bone mass by promoting collagen production and lowering collagen breakdown [47]. Vitamin D is essential for calcium and phosphorus homeostasis, and bone remodeling and its deficiency can also lead to osteopenia and osteoporosis. Low levels of both vitamin D and IGF-1 can increase the risk of falls and fractures which can be another explanation for high fracture rates in cirrhotic patients [47, 49].

The enrolled studies showed considerable heterogeneity in most analyses, which could have influenced the results. We therefore conducted sensitivity analyses to confirm the robustness of this meta-analysis. The results showed that studies with a higher percentage of male participants showed less association between cirrhosis and T-score, osteoporosis, and fracture risk. This relationship was the opposite for femoral neck BMD analysis which might result from men having higher baseline BMDs or different studies included in the analyses. Osteoporosis has a higher prevalence in post-menopausal women who probably constituted most of the female population as the mean age of the included studies suggests [50]. Estrogen, which is essential for maintaining BMD, drops abruptly in women during menopause, whereas, cirrhosis alone does not decrease estrogen levels and in fact, tends to increase it [51–54]. Although other potential confounders, such as comorbidities and medication use, were not consistently reported across studies, making a detailed meta-regression analysis challenging, their potential impact should not be overlooked. Smoking, certain comorbid conditions, such as rheumatoid arthritis, diabetes and tumors, and the use of medications like corticosteroids, estrogens, and supplements can affect osteoporosis risk [55]. Future studies should prioritize standardized reporting of these variables to facilitate more precise assessments of their effects on bone health in cirrhotic patients.

Our sensitivity analysis revealed that neither the average age of the participants nor the study design were sources of heterogeneity for any of the outcomes. The omission of the study by Figueiredo et al. resulted in a high decrease in heterogeneity and made the lumbar T- and Z-score results significant. This finding could be attributed to an older study design and small sample size, as well as other sources of heterogeneity such as different cirrhosis diagnosis criteria and methods, cirrhosis etiology (viral, alcoholic, metabolic, and so on), and cirrhosis severity [27]. Studies with distinct population characteristics also contributed to heterogeneity. Zheng et al. focused exclusively on compensated cirrhotic patients (Child-Pugh A) and had lower BMI, while Gonzalez-Calvin et al. included only postmenopausal women [29, 37]. Removing Chen et al. (2017) increased the OR as it was a large, heavily weighted study that selected the patients based on diagnoses from hospital inpatient care registers which may have led to misplacing patients with minor cirrhosis in the non-cirrhotic group and an underestimation of fracture risk [35]. Although the overall conclusions of our meta-analysis remained consistent after removing these studies, our findings highlight potential subgroup variations and should be interpreted with caution for significantly distinct populations.

Prevention of fractures and early diagnosis of osteoporosis in cirrhotic patients is important as previous studies have shown that patients with liver cirrhosis have higher post-fracture complications and mortality [35]. One study showed that cirrhotic geriatric patients undergoing

surgical repair for hip fracture had worse outcomes such as more non-routine discharges, longer hospital stays, higher complication rates, and higher hospital costs [56]. Given the significant increased fracture risk observed in cirrhotic patients, effective risk stratification and taking proactive measures are necessary.

One possible approach is incorporating cirrhosis severity, as measured by the Child-Pugh or MELD scores, into current fracture risk assessment tools, such as FRAX. Another is to apply an adjustment factor to the FRAX-calculated fracture risk to account for metabolic changes associated with cirrhosis. Future studies should focus on developing a dedicated fracture risk assessment tool tailored to cirrhotic patients for more precise risk stratification.

Targeted screening programs for osteoporosis using dual-energy X-ray absorptiometry (DEXA) scans should be considered, particularly for those with advanced liver disease. Lifestyle modifications, regular weight-bearing exercises and fall-prevention strategies should be integrated into clinical care and can improve patients' quality of life particularly as they approach higher-risk ages. Anti-osteoporotic drugs such as bisphosphonates and denosumab and vitamin D and calcium supplementation can also be considered for high-risk patients [57–60]. Studies and guidelines suggest regular monitoring and maintaining serum 25-hydroxyvitamin D levels above 30 ng/mL in patients with cirrhosis with recommended doses including 5,000 IU/day or 50,000 IU weekly for 3 months in vitamin D deficient individuals followed by 1,000–2,000 IU/day indefinitely [61].

### Strengths and limitations

In this review using a detailed search strategy we conducted a comprehensive literature review with no publication bias and employed advanced meta-analysis methods such as meta-regression and detailed sensitivity analyses to ensure the robustness of our findings. We also assessed multiple bone health outcomes including osteoporosis, fracture risk, and bone mineral density in both the lumbar and femoral regions to gain a comprehensive picture of how cirrhosis influences bone integrity. However, it is important to consider certain limitations. Significant heterogeneity was found between studies, which was most likely caused by differences in cirrhosis etiology, diagnostic methods, and sample demographics. Furthermore, some factors, such as disease severity and co-morbidities, were not consistently reported, which may have influenced generalizability.

## Conclusion

In conclusion, hepatic cirrhosis is associated with a significant increase in the risk of osteoporosis and fractures, highlighting the importance of integration of cirrhosis into clinical fracture-risk models and targeted screening and preventive strategies. Further studies with longitudinal designs are required to assess the risk of osteoporosis based on the etiology and stage of cirrhosis, especially in younger males, as well as to evaluate the efficacy of specific interventions and to develop and validate risk prediction models tailored to cirrhotic patients.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03720-6.

Supplementary Material 1

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**Author contributions**
A.S. = Conceptualization, formal analysis, investigation, methodology, project administration, supervision, validation, writing-review & editing F.M.E. = Conceptualization, data curation, writing-original draft, writing-review & editing D.S. = writing-original draft, writing-review & editing A.A. = Conceptualization, formal analysis, data curation, writing-original draft, methodology Z.F.A. = data curation, methodology S.E. = writing-original draft, writing-review & editing, investigation A.H.H. = Investigation, methodology, validation, writing-review & editing A.G.R. = Conceptualization, investigation, methodology, project administration, supervision, validation, writing-review & editing.

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**Data availability**
Data is provided within the manuscript or supplementary information.

## Declarations

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Not applicable.

**Consent to publish**
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**References**

1. Santos LA, Romeiro FG. Diagnosis and management of Cirrhosis-Related osteoporosis. Biomed Res Int. 2016;1423462.
2. Diab DL, Watts NB. Secondary osteoporosis: differential diagnosis and workup. Clin Obstet Gynecol. 2013;56(4):686–93.
3. Schuppan D, Afdhal NH. Liver cirrhosis. Lancet. 2008;371(9615):838–51.
4. Sepanlou SG, Safiri S, Bisignano C, Ikuta KS, Merat S, Saberifiroozi M, et al. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories,1990–2017: a systematic analysis for the Global Burden of Disease Study 2017.The Lancet Gastroenterology & Hepatology. 2020;5(3):245–66.

5. Lupoli R, Di Minno A, Spadarella G, Ambrosino P, Panico A, Tarantino L, et al. The risk of osteoporosis in patients with liver cirrhosis: a meta-analysis of literature studies. Clin Endocrinol (Oxf). 2016;84(1):30–8.
6. Kang J, Gopakumar H, Puli SR. Prevalence of osteoporosis in cirrhosis: A systematic review and Meta-Analysis. Cureus. 2023;15(1):e33721.
7. Patel N, Muñoz SJ. Bone disease in cirrhosis. Clin Liver Dis (Hoboken). 2015;6(4):96–9.
8. Giouleme OI, Vyzantiadis TA, Nikolaidis NL, Vasiliadis TG, Papageorgiou AA, Eugenidis NP, et al. Pathogenesis of osteoporosis in liver cirrhosis. Hepatogastroenterology. 2006;53(72):938–43.
9. Singer A, McClung MR, Tran O, Morrow CD, Goldstein S, Kagan R, et al. Treatment rates and healthcare costs of patients with fragility fracture by site of care: a real-world data analysis. Arch Osteoporos. 2023;18(1):42.
10. Nazrun AS, Tzar MN, Mokhtar SA, Mohamed IN. A systematic review of the outcomes of osteoporotic fracture patients after hospital discharge: morbidity, subsequent fractures, and mortality. Ther Clin Risk Manag. 2014;10:937–48.
11. University of Sheffield. Fracture risk assessment tool. 2022. Available from: https://www.sheffield.ac.uk/FRAX/
12. Garvan Institute. Bone fracture risk calculator. 2022. Available from: http://au.proxy.cc.uic.edu/bone-fracture-risk
13. ClinRisk. Welcome to the QFracture-2016 risk calculator. 2016. Available from: https://qfracture.org
14. Liang J, Meng WD, Yang JM, Li SL, Zhong MN, Hou XX, et al. The association between liver cirrhosis and fracture risk: A systematic review and meta-analysis. Clin Endocrinol (Oxf). 2018;89(4):408–13.
15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
16. Kanis J. Assessment of osteoporosis at the primary health-care level. Technical Report. http://www.shef.ac.uk/FRAX. 2008.
17. Ma L-L, Wang Y-Y, Yang Z-H, Huang D, Weng H, Zeng X-T. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? Military Med Res. 2020;7(1):7.
18. Porritt K, Gomersall J, Lockwood C. JBI's systematic reviews: study selection and critical appraisal. Am J Nurs. 2014;114(6):47–52.
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.
20. Available from. https://worldpopulationreview.com/country-rankings/hdi-by-country
21. Ghislandi S, Sanderson WC, Scherbov S. A simple measure of human development: the human life Indicator. Popul Dev Rev. 2019;45(1):219–33.
22. Lin L, Chu H. Quantifying publication bias in meta-analysis. Biometrics. 2018;74(3):785–94.
23. Chen CC, Wang SS, Jeng FS, Lee SD. Metabolic bone disease of liver cirrhosis: is it parallel to the clinical severity of cirrhosis? J Gastroenterol Hepatol. 1996;11(5):417–21.
24. Masaki K, Shiomi S, Kuroki T, Tanaka T, Monna T, Ochi H. Longitudinal changes of bone mineral content with age in patients with cirrhosis of the liver. J Gastroenterol. 1998;33(2):236–40.
25. Corazza GR, Trevisani F, Di Stefano M, De Notariis S, Veneto G, Cecchetti L, et al. Early increase of bone resorption in patients with liver cirrhosis secondary to viral hepatitis. Dig Dis Sci. 2000;45(7):1392–9.
26. Casini A, Mohamed EI, Gandin C, Tarantino U, Di Daniele N, De Lorenzo A. Predicting bone mineral density of postmenopausal healthy and cirrhotic Italian women using anthropometric variables. Dig Liver Dis. 2003;35(12):881–7.
27. Figueiredo FA, Brandão C, Perez Rde M, Barbosa WF, Kondo M. Low bone mineral density in noncholestatic liver cirrhosis: prevalence, severity and prediction. Arq Gastroenterol. 2003;40(3):152–8.
28. Wafaa M, Ezzat HMR, Elsherbiny A, Mokhles M. Mohamed Mahmoud Ahmed, Nagwa Abd El-Ghaffar and Enas Abdel Rasheed. bone mineral density and bone turnover markers in chronic liver disease. J Med Sci. 2007;7:748–54.
29. González-Calvin JL, Mundi JL, Casado-Caballero FJ, Abadia AC, Martin-Ibañez JJ. Bone mineral density and serum levels of soluble tumor necrosis factors, estradiol, and osteoprotegerin in postmenopausal women with cirrhosis after viral hepatitis. J Clin Endocrinol Metab. 2009;94(12):4844–50.
30. Ahmed HM, El-Shereef HK, El-Gendi SS, El-Sherif WT, Bakheet MY, Galal GM, et al. Leptin, osteocalcin, and bone mineral density in post-hepatitic liver cirrhosis. Arab J Gastroenterol. 2010;11(3):130–5.
31. Díez-Ruiz A, García-Saura PL, García-Ruiz P, González-Calvin JL, Gallego-Rojo F, Fuchs D. Bone mineral density, bone turnover markers and cytokines in alcohol-induced cirrhosis. Alcohol Alcohol. 2010;45(5):427–30.
32. Goral V, Simsek M, Mete N. Hepatic osteodystrophy and liver cirrhosis. World J Gastroenterol. 2010;16(13):1639–43.
33. Bang UC, Benfield T, Bendtsen F, Hyldstrup L, Beck Jensen JE. The risk of fractures among patients with cirrhosis or chronic pancreatitis. Clin Gastroenterol Hepatol. 2014;12(2):320–6.
34. Culafić D, Djonic D, Culafic-Vojinovic V, Ignjatovic S, Soldatovic I, Vasic J, et al. Evidence of degraded BMD and geometry at the proximal femora in male patients with alcoholic liver cirrhosis. Osteoporos Int. 2015;26(1):253–9.
35. Chen TL, Lin CS, Shih CC, Huang YF, Yeh CC, Wu CH, et al. Risk and adverse outcomes of fractures in patients with liver cirrhosis: two nationwide retrospective cohort studies. BMJ Open. 2017;7(10):e017342.
36. Otete H, Deleuran T, Fleming KM, Card T, Aithal GP, Jepsen P, et al. Hip fracture risk in patients with alcoholic cirrhosis: A population-based study using english and Danish data. J Hepatol. 2018;69(3):697–704.
37. Zheng JP, Miao HX, Zheng SW, Liu WL, Chen CQ, Zhong HB, et al. Risk factors for osteoporosis in liver cirrhosis patients measured by transient elastography. Med (Baltim). 2018;97(20):e10645.
38. Wakolbinger R, Muschitz C, Scheriau G, Bodlaj G, Kocijan R, Feichtinger X, et al. Bone microarchitecture and bone turnover in hepatic cirrhosis. Osteoporos Int. 2019;30(6):1195–204.
39. Chang CH, Chang CJ, Wang YC, Hu CC, Chang Y, Hsieh PH, et al. Increased incidence, morbidity, and mortality in cirrhotic patients with hip fractures: A nationwide population-based study. J Orthop Surg (Hong Kong). 2020;28(3):2309499020918032.
40. Zhang Y, Gao X, Liu T, Gao P, Li H, Liu N, et al. Association between osteoporosis and hepatitis B cirrhosis: a case-control study. Afr Health Sci. 2020;20(4):1610–6.
41. Thakur P, Cherian KE, Kapoor N, Rebekah G, Goel A, Zachariah U, et al. Proximal hip geometry, trabecular bone score, bone mineral density and bone mineral parameters in patients with cryptogenic and hepatitis B related Cirrhosis- A study from the Indian Subcontinent. J Clin Densitom. 2022;25(1):97–104.
42. Katsaounis PV, Hadjiyannis ES, Skaltsi T, Anargyrou VA, Alexopoulou AA, Dourakis SP, et al. Bone disease in patients with cirrhosis of different etiology and severity; are Klotho protein and osteoprotegerin potential biomarkers? Scand J Gastroenterol. 2023;58(2):185–92.
43. Wester A, Ndegwa N, Hagström H. Risk of fractures and subsequent mortality in Alcohol-Related cirrhosis: A nationwide Population-Based cohort study. Clin Gastroenterol Hepatol. 2023;21(5):1271–e807.
44. Guañabens N, Parés A. Osteoporosis in chronic liver disease. Liver Int. 2018;38(5):776–85.
45. van Leeuwen JP, van Driel M, van den Bemd GJ, Pols HA. Vitamin D control of osteoblast function and bone extracellular matrix mineralization. Crit Rev Eukaryot Gene Expr. 2001;11(1–3):199–226.
46. Gallego-Rojo FJ, Gonzalez-Calvin JL, Muñoz-Torres M, Mundi JL, Fernandez-Perez R, Rodrigo-Moreno D. Bone mineral density, serum insulin-like growth factor I, and bone turnover markers in viral cirrhosis. Hepatology. 1998;28(3):695–9.
47. Yuan S, Wan Z-H, Cheng S-L, Michaëlsson K, Larsson SC. Insulin-like growth Factor-1, bone mineral density, and fracture: A Mendelian randomization study. J Clin Endocrinol Metabolism. 2021;106(4):1552–8.
48. Giustina A, Mazziotti G, Canalis E. Growth hormone, insulin-like growth factors, and the skeleton. Endocr Rev. 2008;29(5):535–59.
49. Grover I, Singh N, Gunjan D, Benjamin J, Ramakrishnan L, Pandey RM, et al. Vitamin D status & bone health in patients with liver cirrhosis. Indian J Med Res. 2023;158(3):284–91.
50. Salari N, Ghasemi H, Mohammadi L, Behzadi MH, Rabieenia E, Shohaimi S, et al. The global prevalence of osteoporosis in the world: a comprehensive systematic review and meta-analysis. J Orthop Surg Res. 2021;16(1):609.
51. Weber TJ. Battle of the sex steroids in the male skeleton: and the winner is. J Clin Invest. 2016;126(3):829–32.
52. Shigehara K, Izumi K, Kadono Y, Mizokami A. Testosterone and bone health in men: A narrative review. J Clin Med. 2021;10(3).
53. Vaishnav B, Tambile R, Minna K, Addepalli S, Wadivkar A, Pailla R, et al. Study of gonadal hormones in males with liver cirrhosis and its correlation with Child-Turcotte-Pugh and model for End-Stage liver disease scores. Cureus. 2023;15(1):e34035.
54. Sarkar M, Lai JC, Sawinski D, Zeigler TE, Cedars M, Forde KA. Sex hormone levels by presence and severity of cirrhosis in women with chronic hepatitis C virus infection. J Viral Hepat. 2019;26(2):258–62.

55. Pouresmaeili F, Kamalidehghan B, Kamarehei M, Goh YM. A comprehensive overview on osteoporosis and its risk factors. Ther Clin Risk Manag. 2018;14:2029–49.
56. Tseng F-J, Gou G-H, Wang S-H, Shyu J-F, Pan R-Y. Chronic liver disease and cirrhosis increase morbidity in geriatric patients treated surgically for hip fractures: analysis of the US nationwide inpatient sample. BMC Geriatr. 2022;22(1):150.
57. Jackson C, Gaugris S, Sen SS, Hosking D. The effect of cholecalciferol (vitamin D3) on the risk of fall and fracture: a meta-analysis. QJM. 2007;100(4):185–92.
58. Saeki C, Saito M, Oikawa T, Nakano M, Torisu Y, Saruta M, et al. Effects of denosumab treatment in chronic liver disease patients with osteoporosis. World J Gastroenterol. 2020;26(33):4960–71.
59. Tapper EB, Martinez B, Jepsen P, Chen X, Parikh ND. Bisphosphonate effectiveness in patients with cirrhosis: an emulated clinical trial. Aliment Pharmacol Ther. 2024;60(5):585–92.
60. Adami G, Giollo A, Rossini M, Orsolini G, Benini C, Viapiana O, et al. Different fracture risk profile in patients treated with anti-osteoporotic drugs in real-life. Reumatismo. 2020;72(2):71–4.
61. Konstantakis C, Tselekouni P, Kalafateli M, Triantos C. Vitamin D deficiency in patients with liver cirrhosis. Ann Gastroenterol. 2016;29(3):297–306.

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