Clinical *Standard*

CLINICAL STANDARD · VOL. 1 NO. 1 · 2026
DOI 10.68913/CS.2026.0001 · CC BY 4.0

SYSTEMATIC REVIEW · GENERAL MEDICINE · SURGERY

Chronic Liver Disease and Hip Fracture Risk: A Comprehensive Meta-Analysis of Over a Million Patients

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ABSTRACT

Background. Chronic liver disease (CLD) can impair bone health and has been linked to osteoporosis and fractures, but its association with hip fracture risk remains unclear. This systematic review and meta-analysis summarizes the current evidence on the association between CLD and the risk of hip fracture in adults.

Methods. We conducted this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Four electronic databases (PubMed, Web of Science, Scopus, and Cochrane Library) were searched for cohort studies reporting the risk of hip fracture in adult patients with CLD. Two groups of authors independently performed screening, quality assessment, data extraction, and analysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were pooled using the generic inverse-variance method in Review Manager (RevMan) version 5.1.

Results. Three retrospective cohort studies comprising 1,128,658 adults were included. CLD was not associated with a statistically significant increase in hip fracture risk compared with the non-CLD group (pooled HR 1.34; 95% CI 0.86–2.09; P = 0.20), with considerable heterogeneity across studies (I^2 = 94%). In leave-one-out sensitivity analyses, after excluding the study identified as the main source of heterogeneity, heterogeneity resolved (I^2 = 0%) and the pooled HR remained non-significant (1.04; 95% CI 0.93–1.16; P = 0.53).

Conclusions. The available evidence does not demonstrate a statistically significant association between CLD and hip fracture risk; however, it is limited to three heterogeneous studies and the pooled estimate was imprecise, so no firm conclusion can be drawn. Further research on specific types and severities of CLD is needed to clarify this relationship and to develop guidelines for hip fracture prevention in patients with CLD.

Keywords: Liver Diseases · Hip Fractures · Non-alcoholic Fatty Liver Disease · Hepatitis B · Chronic · Hepatic Encephalopathy · Meta-Analysis

Introduction

The liver performs a multitude of essential bodily functions including the synthesis of clotting factors, protein synthesis, and detoxification of harmful metabolic products, among other functions [1]. Chronic liver disease (CLD) is defined as a decline in liver function that lasts longer than six months [1]. It affects approximately 4% of the global population and increases mortality due to liver-related complications [2]. CLD can be caused by viral infections (such as hepatitis B or C), alcohol abuse, autoimmune disorders, metabolic

diseases, or genetic factors and can lead to many complications, such as cirrhosis, hepatic decompensation, and hepatocellular cancer. Additionally, CLD can negatively impact bone health by increasing the risk of osteoporosis and fracture through various mechanisms, including reduced synthesis of vitamin D and bile acids, impaired calcium absorption and metabolism, increased bone resorption, decreased bone formation, hormonal imbalances, malnutrition, muscle wasting, and use of hepatotoxic drugs [2-8]. When combined with other comorbidities, CLD can lead to increased morbidity, mortality, disability, and healthcare costs [9].

Studies have linked CLD to low bone mineral density, osteoporosis, and fractures; however, data on the impact of CLD on hip fracture risk are limited and inconsistent. Small sample sizes, retrospective designs, and varying definitions of CLD and hip fracture outcomes have contributed to these inconsistencies. To clarify the relationship between CLD and hip fracture risk in adults, a comprehensive systematic review and meta-analysis of the available literature is necessary.

This systematic review and meta-analysis aims to identify all relevant studies that have explored the relationship between CLD and hip fractures in adult patients using defined criteria. This review provides a comprehensive summary of the current evidence on the association between CLD and hip fracture risk in adults. It also identifies knowledge gaps and suggests directions for future research.

Methods

We conducted this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.

Search strategy

We searched four electronic databases (PubMed, Web of Science, Scopus, and Cochrane Library) using specific search terms including “chronic liver disease” and “hip fractures” to find relevant studies published in English from 2013 to 2025. A manual search of the reference lists of published systematic review articles was also performed to identify potentially relevant articles. The full search strategies for all databases are provided in the supplementary material (Supplementary Methods S1).

Study selection and eligibility criteria

Two independent reviewers screened study titles and abstracts for eligibility. Full-text articles of potentially eligible studies were reviewed in detail, with discrepancies resolved through discussion and consultation with a third reviewer, as needed. The inclusion criteria for studies were as follows:

- Study design: observational studies (cohorts).
- Population: adult individuals (18 years or older) of both sexes.
- Exposure: CLD (defined as any chronic liver disease or one of its complications).
- Comparator: adults without CLD.
- Outcome: risk of hip fracture.
- Publication date between 2013 and 2026.

Studies were excluded if they did not fulfill any of the above criteria.

Data extraction and quality assessment

After screening for eligibility, the relevant studies were subjected to bias evaluation and data extraction. Data on the authors, publication year, study design, sample size, population, and outcome assessment were recorded and summarized on a standardized proforma sheet. Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies.

Risk of bias assessment

Using the NOS, two authors evaluated the methodological quality of each study across three domains: selection, comparability, and outcome. Four items in the selection domain evaluated the validity of the selection procedure and the representativeness of the chosen cohort. One item addressing confounding elements comprised the comparability domain. The last three items in the outcome domain evaluated the sufficiency of the follow-up duration and the quality of the outcome measurements.

Publication bias

Egger et al. proposed the funnel plot and Egger's regression test to evaluate publication bias [10]; however, these methods are unreliable when a meta-analysis includes fewer than ten studies. Consequently, we were unable to conclusively determine the presence of publication bias.

Statistical analysis

All statistical computations were performed using Review Manager (RevMan), version 5.1 (The Cochrane Collaboration). Hip fracture risk estimates were pooled as hazard ratios (HRs) with 95% confidence intervals (CIs) using the generic inverse-variance method. To assess heterogeneity, we visually examined forest plots and used the I^2 statistic and the Chi-square test. The Chi-square test determines whether a substantial difference exists between studies, while the I^2 statistic quantifies the degree of heterogeneity in the effect size. Heterogeneity was evaluated and interpreted according to the Cochrane Handbook for Systematic Reviews of Interventions: an alpha level below 0.1 for the Chi-square test indicates significant heterogeneity, and I^2 was interpreted as follows: 0–40%, might not be important; 30–60%, may represent moderate heterogeneity; 50–90%, may represent substantial heterogeneity; and 75–100%, considerable heterogeneity. A random-effects model was used when significant heterogeneity was detected. To ensure that none of the included studies unduly influenced the findings and to verify the statistical reliability of the overall effect size, we performed leave-one-out sensitivity analyses, excluding one study in each instance. No additional methods were required for missing data, as all pooled estimates were extracted directly from the published reports.

Results

Study selection and baseline characteristics

Our initial search identified 217 records, all published between 2013 and 2023. Duplicates were removed using EndNote, and title/abstract and full-text screening were performed using Rayyan [11]. After title and abstract screening, 65 reports were assessed for full-text eligibility. According to the eligibility criteria, three retrospective cohort studies [12-14] with a total of 1,128,658 patients were included in the final analysis. The PRISMA flow diagram shows the search results, study selection steps, and reasons for exclusion (Figure 1). A summary of the included studies is shown in Table 1, and detailed characteristics of the included studies' populations are shown in Table 2.

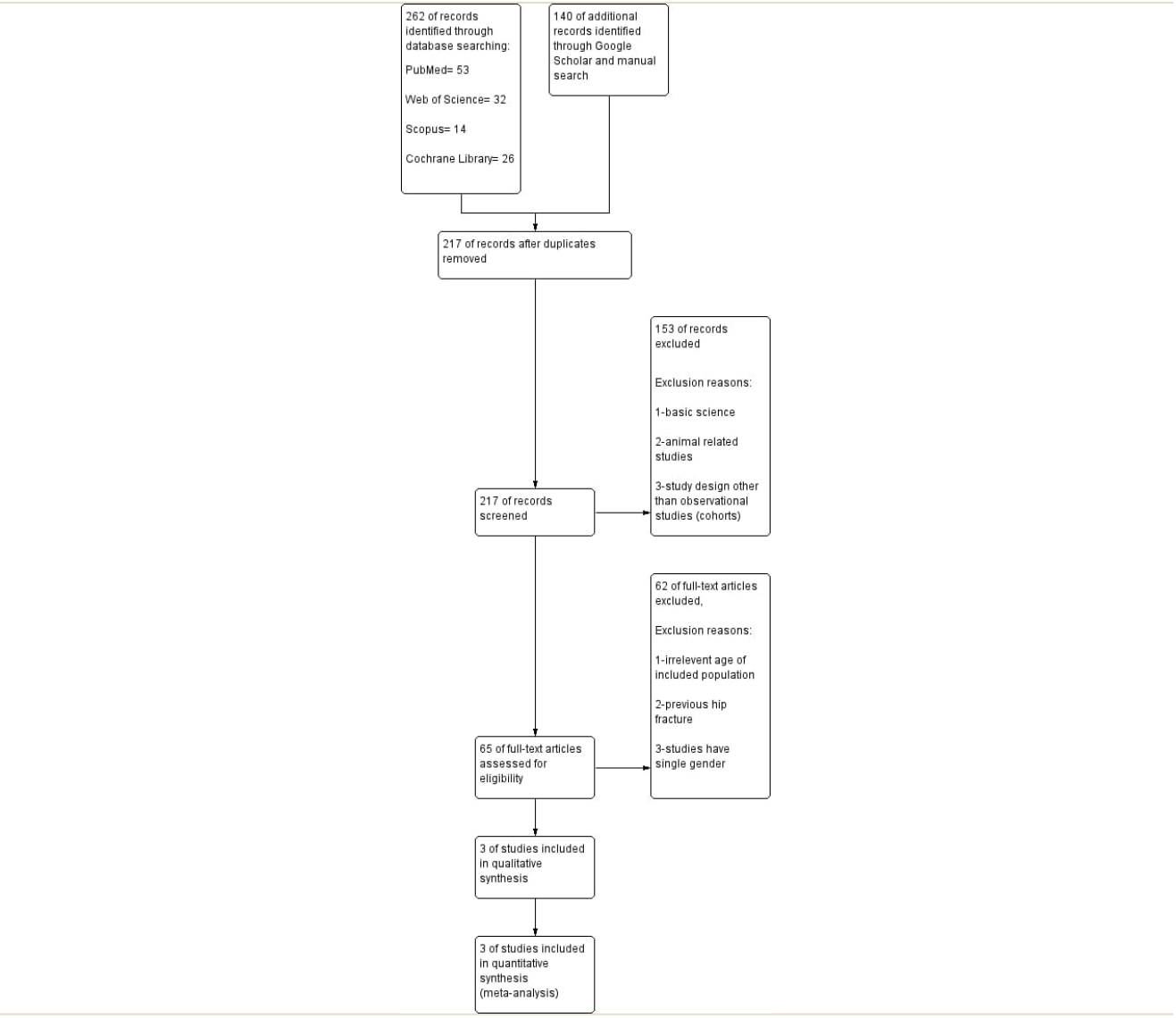


Figure 1 PRISMA 2020 flow diagram of study identification, screening, and inclusion.

Table 1. Summary of the included studies.

Study ID	Population	Sample size	Main outcome	Results
Wester 2022 [12]	NAFLD group vs. control group	109,854	Time of first fracture	NAFLD patients have a slightly higher rate of fractures and long-term risk of fractures comparable to the general population.
Byrne 2014 [13]	CHB-infected group vs. non-infected control group	1,006,324	Incident fracture of the proximal femur (hip)	Untreated CHB-infected patients of black race had a higher risk of hip fracture than uninfected black persons.
Yeh 2020 [14]	HE group vs. control group	12,480	Incidence of osteoporotic hip fracture	HE is significantly associated with an increased risk of osteoporotic hip fractures, and the significance is not affected by comorbidities in people aged more than 50 years. The cumulative risk of fracture increases with age.

NAFLD, non-alcoholic fatty liver disease; CHB, chronic hepatitis B; HE, hepatic encephalopathy. All included studies were retrospective cohorts in design.

Table 2. Baseline characteristics of the included studies.

Study ID	Group	Number	Female, n (%)	Diabetes, n (%)	CKD, n (%)	Alcohol-related illness, n (%)	Rheumatic disease, n (%)	Cancer, n (%)
Wester 2022 [12]	Cases	10,678	5,125 (48%)	1,900 (17.8%)	138 (1.3%)	–	274 (2.6%)	907 (8.4%)
	Controls	99,176	48,024 (48.4%)	3,647 (3.7%)	406 (0.4%)	–	1,026 (1.0%)	5,303 (0.5%)
Byrne 2014 [13]	Cases	26,573	12,626 (45.8%)	2,760 (10.3%)	2,268 (8.5%)	–	873 (3.2%)	1,324 (4.9%)
	Controls	979,751	688,938 (70.3%)	81,742 (8.3%)	35,318 (3.6%)	–	26,438 (2.7%)	29,769 (3.0%)
Yeh 2020 [14]	Cases	2,496	943 (37%)	1,073 (43.0%)	–	537 (21.5%)	–	–
	Controls	9,984	3,708 (37%)	4,446 (44.5%)	–	2,131 (21.3%)	–	–

Comorbidities were recorded at or before baseline.; CKD, chronic kidney disease; –, not reported.

Quality of included studies

The NOS quality ratings were good in all included studies, with scores of 7 or 8 out of 9 (Supplementary Table S1). Participants in all cohorts were accurate representatives of their communities. All studies adjusted for confounding variables such as baseline health issues, diabetes, chronic obstructive pulmonary disease, age, and sex. Most individuals completed their follow-up, and the follow-up duration in all cohorts was greater than 24 months, which is long enough for the relevant event (hip fracture) to develop.

Meta-analysis of the association between CLD and hip fracture

The pooled HR for hip fracture in the CLD group compared with the non-CLD group was 1.34 (95% CI 0.86–2.09; P = 0.20), which was not statistically significant (Figure 2). However, the pooled studies were not homogeneous (Chi-square P = 0.001; I^2 = 94%). The heterogeneity may be due to statistical or methodological factors, such as differing populations, confounding factors, and missing baseline data. To address this, we switched from a fixed-effect to a random-effects analysis and conducted leave-one-out sensitivity analyses (Figure 3). After excluding the study by Yeh et al. (2020) [14], heterogeneity was resolved (P = 0.41; I^2 = 0%) and the pooled HR remained non-significant (HR 1.04; 95% CI 0.93–1.16; P = 0.53).

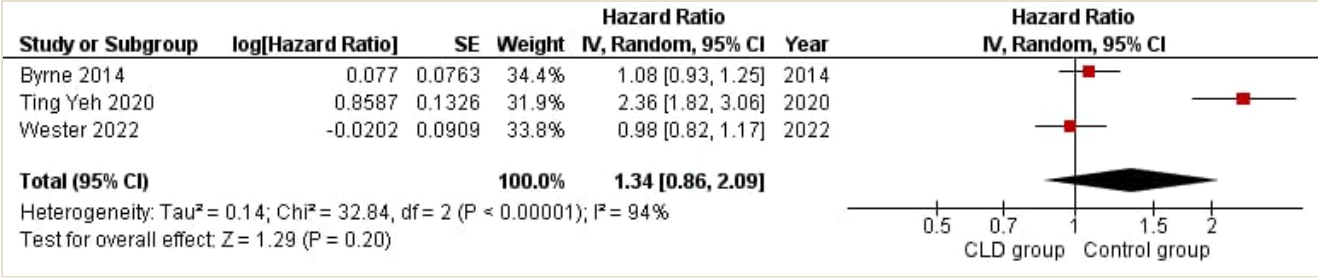


Figure 2 Forest plot of the association between chronic liver disease and hip fracture risk.

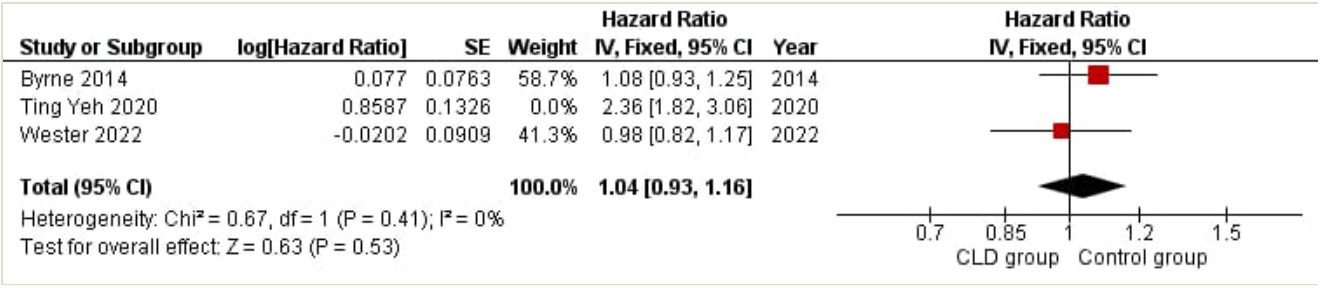


Figure 3 Leave-one-out analysis

Discussion

This meta-analysis of three cohort studies provided pooled data comparing the risk of hip fracture between patients with and without chronic liver disease. The pooled results did not show a statistically significant difference in hip fracture risk between the two groups; however, the width of the confidence interval reflects the low precision of the estimated effect (hazard ratio of hip fracture in CLD patients).

We could not identify published literature that directly compared the risk of hip fracture between patients with and without chronic liver disease in general; however, some studies have discussed specific types of CLD and the risk of fracture in general. Cui R et al. (2013) demonstrated an association between non-alcoholic fatty liver disease (NAFLD) and a higher risk of osteoporosis, and several other studies have reported similar results, for example, Lee DY et al. (2018) and Moon SS et al. (2012). These consistent findings across multiple studies strengthen the evidence for an association between CLD and heightened general bone fracture risk [15-18] and justify the need to directly investigate the relationship between hip fracture and CLD. On the other hand, other studies did not support a connection between CLD and an increased risk of general bone fracture, for example, Kaya M et al. (2013), who suggested that the risk of fracture is connected to other comorbidities including cardiovascular disease and chronic renal disease [19-24].

The processes underlying this association are not fully understood, but it is thought that osteopenia and osteoporosis are highly prevalent in individuals with liver cirrhosis [25]. It is important to consider the occurrence of falls and fall-related injuries in patients with liver cirrhosis, as these can have a negative impact on their health-related quality of life. Various factors contribute to the risk of falls, including minimal hepatic encephalopathy, use of psychoactive drugs, muscle weakness, autonomic dysfunction, hyponatremia, and sleep disorders [26]. Elderly patients with advanced liver cirrhosis may experience fragility fractures due to impaired bone remodeling and decreased bone mass maintenance, which can be aggravated by low levels of insulin-like growth factor-1 [27].

The findings of this study have important clinical implications. More lives need to be saved, particularly those of the elderly, as hip fracture is the most serious outcome of falls in elderly individuals with osteoporosis: 87 to 96 percent of patients suffering hip fractures are 65 years of age or older, and the mortality rate for hip fracture among them is three times higher than that of the general population [28].

The large sample size of our study is a benefit, and several biases were minimized in the included studies. There are some drawbacks to this study. First, there were few papers on this subject, although the large sample sizes of the included studies may partly compensate for this. Second, we could not determine the severity of liver damage or bone condition in the included studies, which is critical to determine diversity across the included studies' populations in terms of baseline characteristics.

Overall, we think that our research can help draw more attention to this important subject and serve as a direction for further investigation.

Conclusion

In conclusion, this systematic review and meta-analysis found that the evidence that patients with chronic liver disease have an increased risk of hip fracture is inconclusive. To better understand the underlying mechanisms and to create practical strategies for preventing hip fractures in this population, more research is required. Clinicians should take the necessary precautions to prevent these complications and be aware of the negative impact of hip fractures on the lives of patients with CLD.

DECLARATIONS

Acknowledgements

This research and manuscript were conducted and prepared entirely by the authors without additional assistance or funding from external contributors.

Funding

No specific funding.

Competing interests

None declared.

Ethical approval

Not applicable. This systematic review and meta-analysis used only previously published data; no ethical approval or informed consent was required.

Data availability

All data generated or analyzed during this systematic review and meta-analysis are from previously published studies, which are cited in the manuscript.

Registration

This review was registered on PROSPERO ID CRD42023402930.

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Received 31 August 2026 **Accepted** 07 October 2026 **Published** 07 October 2026
Citation Eslam Abdelhady, Mohamed Nassar, Ayman A. E. Bahnasy, Abdelziz Abdelaziz Hamoda, Mohamed Abdelhady Elfeky. Chronic Liver Disease and Hip Fracture Risk: A Comprehensive Meta-Analysis of Over a Million Patients. Clinical Standard. 2026;1(1):e1. doi:10.68913/cs.2026.0001
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