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Meta-Analysis of Liver Cirrhosis and The Risk of Fracture

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ABSTRACT

Background: Cirrhosis is the irreversible fibrosis of liver, it continues to be a common cause of morbidity and mortality. It is accompanied by inflammation and malnutrition and thus can have a negative effects on bone metabolism and promote fractures accordingly.

Aim of the study: to evaluate the risk of fractures among patients with cirrhosis.

Methods: A systematic review of the scientific literature following PRISMA/STROBE guidelines, Medline Cochrane Library and Embase abstracts were retrieved using an algorithm comprising relevant MeSH terms from 1980 to 2017. Publications on the association of cirrhosis/bone fracture were abstracted independently by the authors and included in both gender and gender-specific meta-analyses, following recalculations of published data as appropriate. The Newcastle-Ottawa scale was used to evaluate the quality of included studies.

Results: 8 studies met the inclusion criteria enrolling 988 patients (286 of which are diagnosed with alcoholic liver disease (ALD). Overall, ALD demonstrated a relative risk (RR) of 1.825, 95%CI: 1.370-2.28, $\boldsymbol{P} < 0.001$ for the development of bone fractures. Bone mineral density (BMD) was not significantly different between the ALD and control groups, although there was a trend toward lower BMD in patients with ALD. Sensitivity analyses showed consistent results.

Conclusion: in accordance to the present meta-analysis, there is a significant correlation between bone fractures and ALD independent of BMD.

Keywords: Cirrhosis, bone fracture, ALD, chronic Liver Disease, Fibrosis, Orthopedic.

INTRODUCTION

Cirrhosis is defined as a significantly advanced stage of liver fibrosis that can eventually leads to end stage liver disease. It is associated with hepatic vasculature distortion which in turn results in shunting of the portal and arterial blood supply directly into the hepatic outflow (central veins), compromising exchange between hepatic sinusoids and the adjacent liver parenchyma; hepatocytes [(1,2)].

Histologically, it is the development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury. In such condition that the hepatic sinusoids are lined by fenestrated endothelia which rest on a sheet of permeable connective tissue (the space of Disse) which contains hepatic stellate cells (HSC) and some mononuclear cells. The other side of the space of Disse is lined by hepatocytes which execute most of the known liver functions. In cirrhosis the space of Disse is filled with scar tissue and endothelial fenestrations are lost, a process termed sinusoidal capillarization[(1,2)].

Noteworthy, in 2011 it was the 12th leading cause of death in the United States. The main causes of cirrhosis are hepatitis B and C viruses, overuse of alcohol, and nonalcoholic liver disease. The exact prevalence of cirrhosis is unknown, owing to symptom development later in the disease process [(3)]. Alcoholic liver disease (ALD) encompasses a spectrum of injury, ranging from simple steatosis to frank cirrhosis. Typically, symptomatic patients present with advanced liver disease, with concomitant cirrhosis in more than 50%, and superimposed acute decompensation. Even patients with a relatively mild presentation, however, are at high risk of progressive liver injury, with cirrhosis developing in up to 50% [(4)].

Moreover, there is evidence of a clear dose-dependent relation between alcohol intake and the incidence of alcoholic cirrhosis. A daily intake of more than 60 g of alcohol in men and 20 g in women significantly increases the risk of cirrhosis. In addition, steady daily drinking, as compared with binge drinking, appears to be more harmful [(5)].

Bone Fracture causes significant morbidity and mortality, and places an economic burden on societies [(6)]. Although cirrhosis is associated with a broad spectrum of bone diseases, the most common type of bone disease present in hepatic

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osteodystrophy is osteoporosis[7]. Osteoporosis is a disorder characterized by a reduction in bone mass and micro-architectural deterioration of bone tissue with a resultant increased risk of fracture.

Furthermore, it has been suggested that the risk of osteoporosis and associated fractures has been shown to be increased in patients with cirrhosis (irrespective of the etiology) such as ALD, viral cirrhosis, cholestatic liver diseases, and primary biliary cirrhosis [8].

In the present study, we sim to systematically review and meta-analyze the association between liver cirrhosis and bone fracture.

MATERIALS AND METHODS

Data Sources

✓ **Literature search**

The present systematic review is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9].

Data Sources: electronic databases were searched: Scopus, EMBASE , and Google Scholer) , PubMed/MEDLINE, Scopus, The Cochrane Library, and Web of Science. Econlit from 1980 to 2017.

Search terms, phrases, and MeSH terms searched included "Cirrhosis", "Alcoholic liver disease" "chronic liver diseases", "Bone fracture" and "Osteoporosis" , "BMD".A PubMed/MEDLINE search example is ("Cirrhosis"[MeSH]) OR "Alcoholic liver disease" OR "chronic liver diseases" OR "liver fibrosis") AND ("Fracture"[MeSH])).

Authors independently reviewed titles and abstracts and then downloaded relevant studies. References were reviewed for additional studies.

Study Selection and Criteria

Search results were screened by scanning abstracts for the following:

Inclusion Criteria

1- Randomized controlled trials (RCTs), controlled clinical trials (CCTs) and cohort studies
2- Studies published in a peer-review journals
3- Articles assessing liver cirrhosis and ALD in the target and control group
4- Articles included the current study outcome; bone fracture and BMD.
5-

Exclusion Criteria

1- Studies not conducted or translated to English or Arabic languages.
2- Studies with incomplete data
3- Review articles.

Data Extraction

Two reviewers independently reviewed studies, abstracted data, and resolved disagreements by consensus. Studies were evaluated for quality. A review protocol was followed throughout.

Study Quality Assessment

The quality of included trials was assessed by R.O. and J.B. using the Newcastle-Ottawa Scale (NOS) [10], which was modified to fit our study design: 0-3 stars indicate poor study quality, 4-6 stars indicate acceptable study quality, and 7-9 stars indicate good study quality. In the event of disagreements, consensus was reached by discussion.

Meta-Analysis

We used the statistical package Comprehensive Meta-Analysis [11], version 2.2.064 (Biostat, Englewood, CO) for our analyses.

Individual study proportions were assessed at 95 % confidence interval (CI) as well as the pooled effect. Test for heterogeneity was performed for all the proportions based on Cohran's Q and degree of inconsistency (I2) [12]. In all the summary or pooled analysis, random effect model was adopted over fixed effect model due to the presence of heterogeneity resulting from variations of effects from individual studies confirmed by $I2 > 0$ %. For all computations, statistical significance was set at $p < 0.05$. We conducted sub-analyses for the periods within which studies were published among diverse population sub-groups.We used the random effects model in order to pool the effect sizes and calculate the standardized mean difference (SMD) and the 95% confidence interval from the mean and standard deviation.

RESULTS

Searches identified 871 publications in addition to another 19 publications that were found through manual research. After removal of duplicates, abstracts and titles 301 publications were assessed as identified from title and abstract, and 192 papers were excluded. 13 papers full text could not be retrieved and another 45 papers with the same cohort. There were also 43 papers excluded because they did not include one of the study outcome (bone fracture, osteoporosis or/and BMD).

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in reporting the results. **Figure 1**

Finally, 8 studies were included and detailed as the focus for the present study.

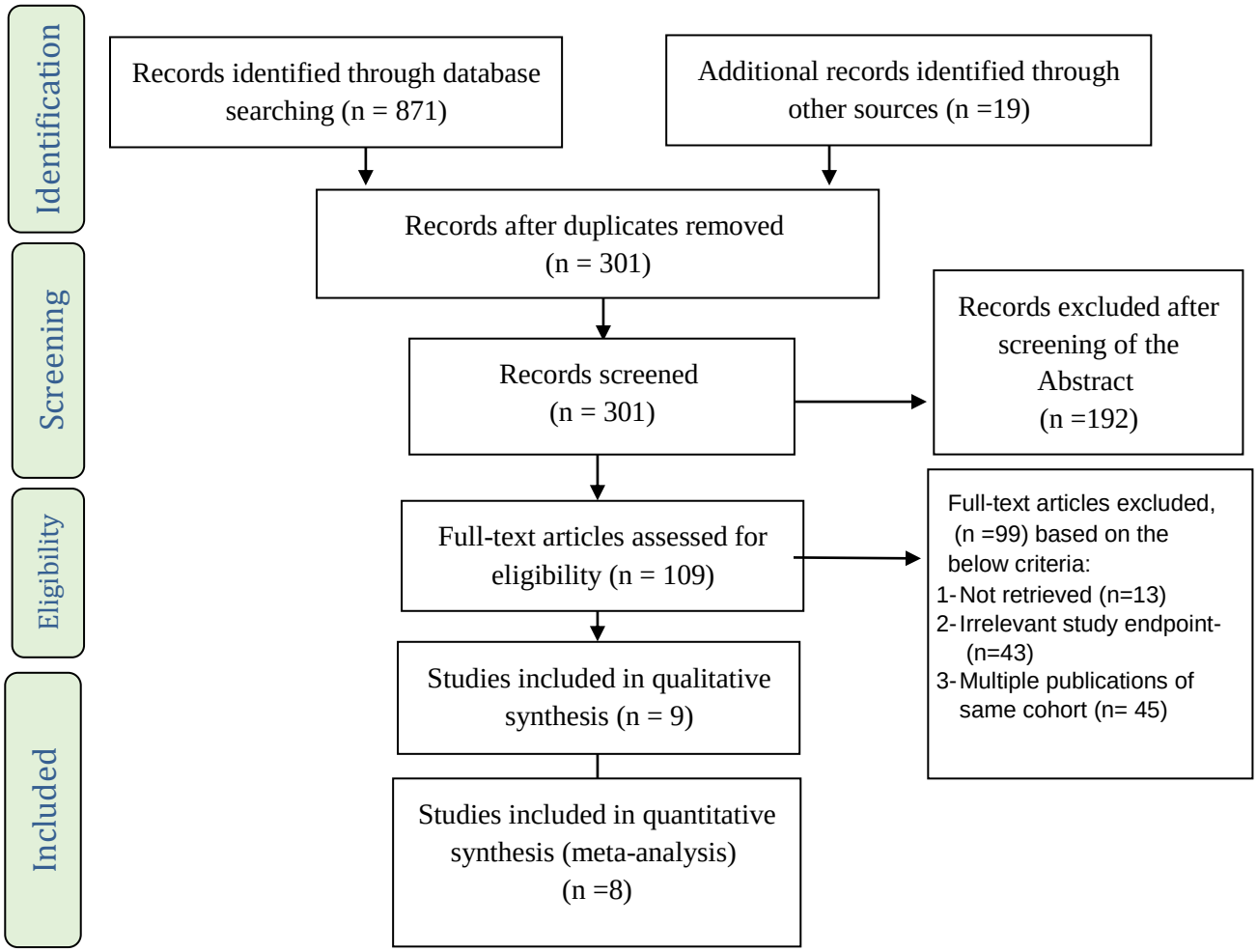

Figure 1: PRISMA flow diagram showing the selection criteria of assessed the studies [9].

Characteristics of the included studies

In 8 studies, we identified a total of 1065 participants (388 patients with ALD vs 413 controls) in the analysis of bone fractures, 470 participants (260 patients with ALD vs 210 controls) in the analysis of osteoporosis, and 769 participants (391 patients with ALD vs 378 controls) in the analysis of BMD. The clinical characteristics of the enrolled studies are shown in Table **1**

Table 1: Baseline Characteristics of the included studies

Authors	Year of Publication	Mean Age	Sample Size	Liver Disease
González-Reimers et al. [13]	2011	Mean age: 50.5 ± 11.23, 38 Controls (Mean age: 48.47 ± 11.08)	124	ALD
Mahmoudi et al. [14]	2011	Mean age: 55.3 ± 11.4, F: 37, mean age: 65.2 ± 11	109	CLD
Wibaux et al. [15]	2011	Mean age: 55 ± 8	99 (M: 79, F: 20)	CLD
González-Reimers et al. [16]	2011	Mean age: 50.14 ± 10.49, 30 normal controls (Mean age: 50.11 ± 10.4)	90	ALD
Sokhi et al. [17]	2004	Mean age: 54.4 ± 12.9	104 (**M: 54, F: 50)**	CLD
Carey et al. [18]	2003	Mean age: 51, range: 32-68	20 7(M: 131, F: 76)	CLD (66 ALD, 73 HCV + ALD, 68 HCV)
Ninkovic et al. [19]	2001	Mean age: 51.1 ± 10.9	243 (M: 128, F: 115)	CLD
Ninkovic et al. [20]	2000	Mean age: 51.3, range: 32-65	37 (M: 20, F: 17)	CLD (6 ALD, 31 other CLD)

Table 2: Clinical data of the included studies

Authors	Liver Disease	Liver cirrhosis in ALD	Bone fractures				
			Fracture site	ALD fracture	Total ALD	Control fracture	Total control
	ALD	51 ALC, 61 Non-LC			124		38 (normal control)
***Mahmoudi** et al.* [14]	CLD	All (31)			31		43 (LC-HCV)
***Wibaux** et al.* [15]	CLD	All (39)	Vertebra	17	39	19	60 (other CLD)
***González-Reimers** et al.* [16]	ALD	40 ALC, 48 Non-LC	Overall fractures	49	90	0	30 (normal control)
***Sokhi** et al.* [17]	CLD	All (17)			17		69 (LC-HCV)
***Carey** et al.* [18]	CLD (66 ALD, 73 HCV + ALD, 68 HCV)	NA	Overall fractures	21	66	13	68 (HCV)
***Ninkovic** et al.* [19]	CLD	Predominantly LC			46		55 (HCV)
***Ninkovic** et al.* [20]	CLD (6 ALD, 31 other CLD)	NA	Vertebra	6	6	17	31 (other CLD)

ALD: Alcoholic liver disease; BMD: Bone mineral density; CLD: Chronic liver disease

META-ANALYSIS

The cumulative meta-analysis of the included studies in the order of published year showed a decreasing trend of RRs, but a consistent and statistically significant increase in bone fractures.

In the sensitivity analyses of high-quality [18,19] and low-quality [13,15] studies for bone fractures, consistent results were noted (RR = 1.758, 95%CI: 1.306-2.208, ***P*** < 0.001; RR = 1.998, 95%CI: 1.216-2.781, *P* = 0.001). When compared to Control subjects, it has been found that the association between ALD and bone fractures was statistically significant both in studies utilizing the normal healthy population as the control arm [13]. In the analysis of the association between ALD and bone fractures, the outlier was noted to have an effect size of 32.687 (RR). After excluding this outlier [13] in the analysis of the association between ALD and bone fractures, the result was unchanged and was statistically significant (RR of 1.825, 95%CI: 1.370-2.28, *P* < 0.001).

DISCUSSION

In the present meta-analysis, bone fracture was commonly associated with Cirrhosis and especially attributed to ALD. This emphasizes that there is a possibility that the fractures occurring in patients with ALD could be BMD-independent in the first place.

In contrast, we didn't observe attribution between the clinical severity of the cirrhosis and BMD as concluded by **Chen *et al.*** [21].

However, a study conduected by **Djonic *et al.*** [26] reported a lower areal BMD, cross sectional area and section modulus, thinner cortex and higher buckling ratio in neck region of patients with cirrhosis suggest increased risk for fracture. Particular affection of cervical region is consonant with epidemiological data indicating more cervical than trochanteric fractures in elderly males.

Nevertheless, **Bonkovsky *et al.*** [8] studied patients with chronic liver diseases of different underlying causes and reported a prevalence of osteopenia (defined as a BMD <2 SD below that of age- and sex-matched controls) ranging from 13 to 39%.

Similarly, **Diamond *et al.*** [22] reported a prevalence of spinal osteoporosis (defined as a BMD <2 SD below that of age- and sex-matched controls) of 16% among patients and of 7% among controls.

The loss of bone mass in cirrhosis is obviously multifactorial, and several risk factors are involved such as changes in parathyroid hormone (PTH) concentrations which can influence the development of osteoporosis in patients with liver cirrhosis irrespective of the cause of the cirrhosis[22] . **Kirch *et al.*** [23] found elevated PTH44-68 serum levels (the median region of the PTH molecule) to be correlated with

severity of liver disease. Serum PTH44-68 may be elevated in patients with cirrhosis who do not have parathyroid hyperfunction because the liver is responsible for cleavage of I-PTH and for clearance of its inactive metabolites. As suggested by **Duarte *et al.*** [24], the liver's reduced capacity to clear PTH metabolites may cause PTH44-68 elevation in patients with advanced liver disease. There are conflicting results regarding the correlation of serum PTH levels and BMD values in chronic liver disease patients. **Bonkovsky *et al.*** [8] did not find any significant correlation between BMD values and serum PTH levels. In contrast, **Crosbie *et al.*** [25] reported a significant correlation between serum PTH levels and BMD values.

Regarding the quality if the included studies, a major factor to be considered is the quality of the included studies which were mainly classified into either high-quality studies with score more than or equal to 7 stars or low-quality studies with score less than 7 stars. This standard was determined by the authors. However, notwithstanding the drawbacks of methodological quality, the sensitivity analyses divided by study quality still showed consistent results.

Nevertheless, further high-quality studies are crucially needed for the broad application of such results.

Furthermore, a significant outlier [13] was observed during the main and sensitivity analyses. To explain, in the analysis of the correlation between ALD and bone fractures, the effect size of the outlier exceeded 10 times of the size of the adjusted effect. We therefore excluded the outlier in the second analysis and consistent results were demonstrated. The drivers behind this huge impact of the outlier was due to a methodological problem since the presence of fracture was recorded by anamnesis and chest X-ray film [13] in this study. This inaccurate methodology could overestimate the rate of bone fractures. Moreover, the quality measured by NOS was low (6 stars) in this study.

CONCLUSION

A strong body of evidence suggests a significant association between bone fractures and ALD, independent of BMD or the presence of osteoporosis. Due to the qualitative and quantitative heterogeneity among studies, further studies utilizing homogenous populations and controlling for confounding risk factors for fractures are needed to elucidate the underlying mechanism of bone fractures in ALD.

REFERENCES

1. **Schuppan D, Afdhal NH(2008):** Liver cirrhosis. The Lancet,371(9615):838-51.
2. **Schaffner H, Popper H(1963):** Capillarization of the sinusoids. Gastroenterology,44:339–42.
3. **Tsochatzis EA, Bosch J, Burroughs AK(2014):** Liver cirrhosis. *Lancet*,383:1749-1761.
4. Bird GL, Williams R(1998) Factors determining cirrhosis in alcoholic liver disease. Mol Aspects Med .,10:97-105
5. **Grant BF, Dufour MC, Harford TC(1988):** Epidemiology of alcoholic liver disease. *Semin Liver Dis* .,8(1):12-25.
6. **Mounach A, Ouzzif Z, Wariaghli G *et al.*(2008):** Primary biliary cirrhosis and osteoporosis: a case-control study. J Bone Miner Metab .,26:379–84.
7. **Boulton-Jones JR, Fenn RM, West J, Logan RF, Ryder SD(2004):** Fracture risk of women with primary biliary cirrhosis: no increase compared with general population controls. Aliment Pharmacol Ther., 205:551–7.
8. **Bonkovsky HL, Hawkins M, Steinberg K *et al.* (1990):** Prevalence and prediction of osteopenia in chronic liver disease. Hepatology,12:273–80.
9. **Moher D, Liberati A, Tetzlaff J, Altman DG (2009):** *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: PLoS Med., 6(7): e1000097.
10. **Wells GA, Shea B, O'connell D, Peterson J, Welch V, Losos M, Tugwell P(2009):** The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available from: URL: http://www. ohri. ca/programs/clinical_epidemiology/oxford. htm
11. **Pierce CA (2008):** Software Review: Comprehensive Meta-Analysis (Version 2.2. 027).Biostat. Organizational Research Methods, 11(1):188-91
12. **Higgins JPT, Thompson SG, Deeks JJ, Altman DG(2003):** Measuring inconsistency in meta-analyses. Br Med J., 327(7414):557–60.
13. **González-Reimers E, Alvisa-Negrín J, Santolaria-Fernández F *et al.* (2011):** Prognosis of osteopenia in chronic alcoholics. Alcohol., 45:227–238.
14. **Mahmoudi A, Sellier N, Reboul-Marty J *et al.* (2011):** Bone mineral density assessed by dual-energy X-ray absorptiometry in patients with viral or alcoholic compensated cirrhosis. A prospective study. Clin Res Hepatol Gastroenterol. ,35:731–737.
15. **Wibaux C, Legroux-Gerot I, Dharancy S*et al.* (2011):** Assessing bone status in patients awaiting liver transplantation. Joint Bone Spine. ,78:387–391.
16. **González-Reimers E, Alvisa-Negrín J, Santolaria-Fernández F *et al.* (2011):**Vitamin D and nutritional status are related to bone fractures in alcoholics. Alcohol Alcohol., 46:148–155.
17. **Sokhi RP, Anantharaju A, Kondaveeti R*et al.* (2004):**Bone mineral density among cirrhotic patients awaiting liver transplantation. Liver Transpl., 10:648–653.
18. **Carey EJ, Balan V, Kremers WK, Hay JE(2003):** Osteopenia and osteoporosis in patients with end-stage liver disease caused by hepatitis C and alcoholic liver disease: not just a cholestatic problem. Liver Transpl. ,9:1166–1173.
19. **Ninkovic M, Love SA, Tom B, Alexander GJ, Compston JE (2001):** High prevalence of osteoporosis in patients with chronic liver disease prior to liver transplantation. Calcif Tissue Int. ,69:321–326.

20. **Ninkovic M, Skingle SJ, Bearcroft PW*et al.* (2000):**Incidence of vertebral fractures in the first three months after orthotopic liver transplantation. Eur J Gastroenterol Hepatol., 12:931–935.
21. **Chen CC, Wang SS, Jeng FS, Lee SD(1996):** Metabolic bone disease of liver cirrhosis: is it parallel to the clinical severity of cirrhosis? J Gastroenterol Hepatol.,11:417–21.
22. **Diamond T, Stiel D, Lunzer M*et al.* (1990):** Osteoporosis and skeletal fractures in chronic liver disease. Gut,31:82–7.
23. **Kirch W, Höfig M, Ledindicker T, Schmidt-gayk H(1990):** Parathyroid hormone and cirrhosis of the liver. J Clin Endocrinol Metab., 16:1561–6.
24. **Duarte MP, Farias ML, Coelho HS *et al.* (2001):** Calcium parathyroid hormone-vitamin D axis and metabolic bone disease in chronic viral liver disease. J Gastroenterol Hepatol.,16:1022–7.
25. **Crosbie OM, Freaney R, McKenna MJ, Hegarty JE(1999):** Bone density, Vitamin D status, and disordered bone remodeling in end-stage chronic liver disease. Calcif Tissue Int.,64:295–300.
26. **Djonic D, Culafic D, Culafic-Vojinovic V, Ignjatovic S, Soldatovic I, Vasic J, Djuric M(2013):** Bone fragility in patients with alcoholic liver cirrhosis: can hip structure analysis better predict risk of hip fracture. *Bone Abstracts, 1.PP334.* DOI:10.1530/boneabs.1.PP334