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Original Article

Investigation of the influential factors for hepatic osteodystrophy in chronic liver disease: A case–control survey among the patients attending a tertiary care hospital in a rural region of Northern India

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Abstract

Objectives: Hepatic osteodystrophy (HOD) is a well-recognized complication of chronic liver diseases (CLD), but the influential factors associated with this complication were studied scarcely in a rural Indian population. The study aims to evaluate the prevalence of HOD and variables that might influence it among cases diagnosed with CLD. **Materials and Methods:** It is a cross-sectional observational design survey that was performed in a hospital among the two-hundred cases and controls with a 1:1 ratio who were age (>18 years) and gender matched in a period between April and October 2021. They were subjected to etiological workup, hematological and biochemical investigations, and Vitamin D levels. Then, dual-energy X-ray absorptiometry was used to measure the bone mineral densitometry (BMD) for whole-body, lumbar spine (LS), and hip. HOD was diagnosed according to the WHO criteria. Then, the Chi-square test and conditional logistic regression analysis were used to investigate the influential factors of HOD in CLD patients. **Results:** The whole-body, LS-spine, and hip BMDs in CLD cases were found to be significantly lower as compared to controls. When the participants among both groups were stratified by age and gender, a significant difference in LS-spine and hip BMD was observed in elderly patients (>60 years), and in both the male and female patients. HOD was found in 70% of CLD patients. After multivariate analysis in CLD patients, we identified that being a male patient (odds ratio [OR] = 3.03), older age (OR = 3.54), duration of illness for more than 5 years (OR = 3.89), decompensated liver dysfunction with Child–Turcotte–Pugh-B and C grading (OR = 8.28), and low level of Vitamin D (OR = 18.45) were the risk factors for HOD. **Conclusion:** This study concludes that severity of illness and lower level of Vitamin D were the main influential factors for HOD. Supplementation of Vitamin D and calcium in the patients can abate the risk of fractures in our rural communities.

Keywords: *Bone mineral density, Chronic liver disease, Hepatic osteodystrophy, Risk factors*

Introduction

Chronic liver disease (CLD) is a highly prevalent entity estimated among 1.5 billion people and a notable cause of death all over the globe [1]. In 2017, CLD contributed to a higher mortality rate (2.2%) and disability-adjusted life-years (1.5%) across the globe [2]. In India, 33.9% of CLD patients presented with decompensated cirrhosis [3]. In recent years in the light of the promptly economic growth, with modifications in nutrition and lifestyle, it is speculated that the etiological determinants and spectrum of CLD might have changed [4]. For instance, alcoholic liver diseases (ALD) are still contributing to higher morbidity (34%), and the magnitude of non-ALD has declined significantly by 26% in India [3,4]. A few studies have demonstrated the increased susceptibility of metabolic bone diseases as extrahepatic complications manifested in the form of osteoporosis and rarely osteomalacia, both combined are known as hepatic osteodystrophy (HOD) [5,6]. Recently, the magnitude of osteoporosis has been found to be increasing in LD

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patients [7]. These represent a major health burden, including long-term disability, inferior quality of life, increased mortality rate, and high health-care expenses [2,8]. Therefore, early identification of low bone mineral densitometry (BMD) is needed to reduce the burden of fragility fractures.

Recently, a few studies over the years have demonstrated that the mechanism related to the development of HOD among CLD patients was found to be complex [8-10]. In addition, the mechanism backstage of this phenomenon is not entirely acknowledged, and chronic inflammation, insulin resistance, and Vitamin D deficiency seem to provide possible relatedness [11,12]. Obvious from the present literature, the prevalence of HOD in CLD patients has a wide range which varies from 12% to 71% in Western countries [13,14], and osteoporosis is common among these patients irrespective of disease etiology [10,15]. Furthermore, in patients with advanced CLD, a much higher prevalence (55%) of osteoporosis was reported, with a fracture rate of 3%–44% [16,17]. The huge variations in prevalence may be ascribed to the ambiguous definition of osteoporosis in patients with CLD [11-17]. The prevalence of HOD varies pursuant to the type and progression of CLD accompanying a myriad of multiple contributing factors incorporating the ethnicity of the community studied; hence, it is probably multifactorial [18]. Previously, it has been established that sex, age, body mass index (BMI), alcohol drinking, tobacco smoking, and poor nutritional status were risk factors for the development of HOD in CLD patients [10,19,20]. In addition, few studies revealed some conflicting results regarding the association between HOD and the severity of CLD [21]. Hence, to reverse the predisposing risk factors, it is important to make a diagnosis in the preliminary phase of CLD. In context to this, multiple researches had been performed among the Western population [12,16,19-21] to evaluate the risk factors for HOD, but very scarce knowledge is available from the Indian rural scenario [10,15,18]. Therefore, the present case–control survey was formulated to determine the magnitude and influential factors for HOD and also to characterize HOD in CLD patients, in a resource-restrained setting in a rural area of northern India.

Materials and Methods

Study design and settings

This case–control cross-sectional and observational survey was conducted in the Medicine Department at Bhagat Phool Singh Government Medical College for Women, which is a 540-bed teaching hospital located in a rural area of North India. This tertiary care hospital provides health-care services to around 500,000 outpatients and 25,000 inpatients in a year. This study was conducted from April to July 2021 after getting ethical approval from the Institutional Ethical Committee Board (BPSGMCW/RC 578/IEC/2020; Dated: October 23, 2020) and in accordance with Ethical Committee Standards and the Helsinki Declaration. Around 200 patients from inpatient and outpatient settings provide written informed consent before enrollment in the study.

Inclusion criteria

All patients aged ≥18 years, presented to OPD and were admitted to the department of medicine, and who were willing to provide informed consent were enrolled in the present study. The diagnosis of CLD was based on the clinical profile, ultrasonography (USG) of the abdomen, and liver function tests (LFTs). Patients with one or more of the aforementioned manifestations suggestive of CLD, i.e., hypoalbuminemia (serum albumin level 3.5 mg/dL) in addition to any clinical confirmation of portal hypertension (variceal bleed, ascites with or without spontaneous bacterial peritonitis, or who have recovered from hepatic encephalopathy) and/or USG abdomen showing altered echotexture provides evidence of fatty liver, chronic hepatitis, cirrhosis or biopsy result consistent with chronic hepatitis or cirrhosis, were defined as cases [22].

Exclusion criteria

Patients with age under 18 years, pregnancy, noncirrhotic portal fibrosis, multiple metastases, obvious focal hepatic disease (cholangiocarcinoma, hydatid cysts, hepatocellular carcinoma, and liver abscess), malabsorption diseases, glucocorticoids/steroids/medications for osteoporosis/Vitamin D supplementation, diabetes, early surgical menopause, parathyroid and thyroid dysfunction, renal failure, Cushing's syndrome, and premature ovarian/testicular failure were excluded from the study. The other excluded cases were those who did not provide consent to the study.

Sampling and data collection procedure

A consecutive sampling procedure was applied to get 100 cases of CLD as per the case definition. Baseline characteristics and clinical data were recorded for all patients. Then, all the participants with suspected CLD underwent complete hemogram evaluation, LFT (alanine transaminase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, serum bilirubin [total, indirect, and direct], serum albumin, and globulin), and serum Vitamin D in the central clinical laboratory. Finally, participants underwent imaging of the abdomen to scrutinize liver echotexture, liver dimensions, and features of portal hypertension (portal vein diameter, ascites, and splenomegaly) [Figure 1].

Healthy controls were randomly selected from medicine OPD who were willing to participate in the study. Healthy controls included in the study were those who have matched with cases in respect of age (within 5 years) and same gender. The controls who had a previous history of any hepatic disease were excluded from the study.

Data collection measures

All cases and controls were examined about the potentially influential variables of HOD through a semi-structured, precoded, and pretested questionnaire. Before the data collection procedure, participants were briefed about the purpose of the survey along with an assurance of maintaining the privacy and confidentiality of their information given to the researchers. The interviews were conducted in the local language (Hindi) to elicit the required information from all the participants. Data were collected in the form of

sociodemographic factors, biochemical parameters, etiological factors, the severity of illness, and bone mineral density.

Sociodemographic factors were regarding current age, gender (male/female), and duration of illness (in years). Biochemical parameters (LFTs) such as serum bilirubin (total), serum albumin, AST, ALT, and serum Vitamin D were recorded separately. The etiology of CLD patients was determined as per the standard clinical protocols. For the present study, participants showing positive test results for hepatitis B/C surface antigen were labeled as hepatitis B/C positive. The participants who provided the details about the high amount of alcohol consumption (60–80 g of alcohol per day for men and 40–60 g per day for women for 10 years or more) along with raised serum aminotransferase levels without other causes of liver disease were conjectured to have ALD. The participants who had CLD along with obesity (BMI >25) or diabetes mellitus in the absence of evidence of any other etiology, such as excessive alcohol use, increased transferrin saturation, or a positive Hepatitis B or hepatitis C test were considered to have nonalcoholic steatohepatitis (NASH). Child–Turcotte–Pugh (CTP) scores were used for the severity/clinical staging of CLD: Class A (5–6) for good hepatic function, Class B (7–9) for moderately impaired, and Class C (10–15) for advanced hepatic dysfunction, including 5 μm indicators: ascites, hepatic encephalopathy, total bilirubin, prothrombin time extension, and serum albumin [23]. BMD was determined by dual-energy X-ray absorptiometry (DEXA) using an Osteocore 3 densitometer (Medilink Inc., France). Measurement sites were the lumbar spine (LS) (L1-L4) and the femoral neck. The measurements were reported as a T-score, which is defined as the number of standard deviations (SD) above or below the mean bone density of a healthy adult of the same sex. As per the criteria set by the World Health Organization, patients with a T-score between − 1 and − 2.5 SD and below-2.5 SD in at least one of the three skeletal sites (LS, femur neck, or total hip) were considered to have osteopenia and osteoporosis, respectively. In addition, HOD or low BMD was stated as the presence of osteopenia or osteoporosis (T-score below −1 SD) [24,25]. In this study, osteoporosis and osteopenia were defined with a T-score of two skeletal sites (LS and total hip).

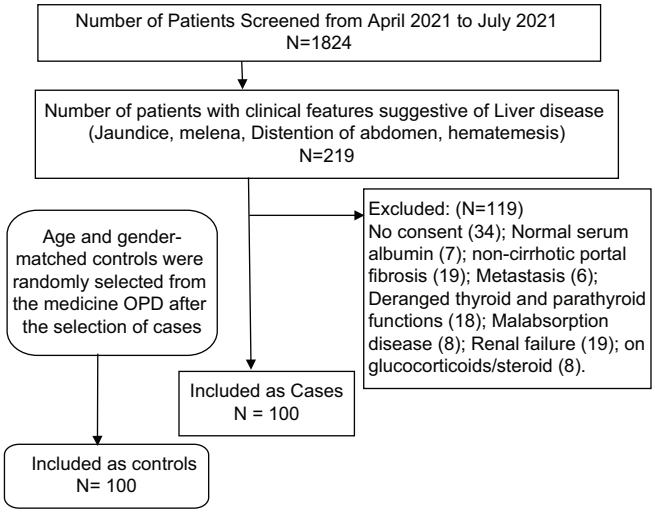

Figure 1: Flowchart of study subjects (cases and controls)

Statistical analysis

SPSS statistical software package 25.0 (IBM, Chicago, IL, USA) was used to interpret the data collected in the study. Statistical information that consisted of continuous variables was represented as means and SD. Continuous data displayed a skewed distribution by the Shapiro–Wilk test was evaluated using a Mann–Whitney U-test. The Chi-square test was adopted for comparing the proportion involving categorical groups. Conditional logistic regression analysis was executed to determine the significant variables that were independently associated with HOD with the implementation of odds ratio (OR) and 95% confidence interval (95% CI). A statistically significant level was set at $P < 0.05$ (two-tailed).

Results

Around two hundred subjects matched for age and gender participated in this study as cases and controls with a ratio of 1:1. Their baseline characteristics are depicted in Table 1. The mean value of biochemical parameters and BMD score of subjects are depicted in Table 2, in which serum bilirubin levels, AST, and ALT were significantly ($P < 0.001$) higher, and serum albumin and serum Vitamin D levels were significantly lower ($P < 0.001$) in cases than that of controls. The mean score of whole-body BMD, hip BMD, and LS-spine BMD in cases was significantly ($P < 0.001$) lower than that of controls.

The association between bone mineral densitometry and sociodemographic factors

In both CLD patients and healthy controls, greater age (>60 years) was associated with lower BMDs, and

Table 1: Baseline demographic characteristics of the cases and controls

Variables	Subgroups	*n* (%); Mean±SD		*P* (Mann–Whitney *U*-test)
		Cases (*n*=100)	Controls (*n*=100)	
Age	Mean age	52.12±11.60 years	52.12±11.60 years	0.992
	<40 years	16 (16)	16 (16)	
	40–60 years	56 (56)	56 (56)	
	>60 years	28 (28)	28 (28)	
Gender	Male	62 (62)	62 (62)	1.000
	Female	38 (38)	38 (38)	
Duration of CLD	Mean duration	7.18±3.14 years		
	≤5 years	30 (30)		
	>5 years	70 (70)		
Type of CLD	Hepatitis B/C	48 (48)		
	ALD	36 (36)		
	NASH	16 (16)		
Severity of illness (CTP grading)	A	38 (38)		
	B	34 (34)		
	C	28 (28)		

CLD: Chronic liver disease, ALD: Alcoholic liver disease, NASH: Nonalcoholic steatohepatitis, CTP: Child–Pugh–Turcotte, SD: Standard deviation

younger age (<40 years) was associated with higher BMDs. Male had greater BMDs than females. The difference in whole-body, hip, and LS-spine BMDs between the CLD patients and controls were significant ($P < 0.001$) in both male and female. For all the three stratified subpopulations based on age, the whole-body BMD score was significantly ($P < 0.001$) lower in patients with CLD than that in controls. The significant ($P < 0.05$) difference for LS-spine BMD score was observed only for the elderly age subpopulation, as shown in Table 3.

The association between bone mineral densitometry and duration, etiology, and severity of chronic liver diseases

In intragroup analysis among cases, no significant difference was observed for various BMDs measured in the study when they were stratified by duration of illness (≤5 years and >5 years), while on stratification by etiology into two subgroups, including ALD and non-ALD (NAFLD; consisting of HBV, HCV, and NASH) in which only whole-body BMD was significantly affected in ALD patients (0.93 ± 0.20 vs. 1.01 ± 0.16; $P < 0.05$) than that of patients with NAFLD. Similarly, all the cases were stratified by severity of illness into patients having a nondecompensated liver function (CTP Grading A) and decompensated liver function (CTP Grading B and C) subgroups. For patients having decompensated liver function, both the whole-body BMD (0.89 ± 0.16 vs. 1.07 ± 0.18; $P < 0.001$) and hip BMD (0.97 ± 0.27 vs. 1.11 ± 0.31; $P < 0.05$) were significantly lower than that of patients with nondecompensated liver, although there was no significant difference observed for spine BMD.

Table 2: Comparison of biochemical parameters and bone mineral densities between chronic liver disease cases and the control group

Variables	Mean±SD		*P* (Mann–Whitney *U*-test)
	Cases (*n*=100)	Controls (*n*=100)	
Serum bilirubin (total) (normal≤1.2 mg/dL)	2.49±1.46	1.03±0.35	<0.001**
serum Albumin (normal≤3.4 gm/dL)	2.99±0.93	3.78±0.59	<0.001**
AST (Normal up to 45 U/L)	68.10±26.00	42.50±8.71	<0.001**
ALT (Normal up to 60 U/L)	89.80±16.42	58.60±10.47	<0.001**
Serum Vitamin D (Normal>20 ng/mL)	14.62±3.21	26.94±8.22	<0.001**
Whole-body BMD (kg/m^2)	0.96±0.19	1.13±0.18	<0.001**
Hip BMD (kg/m^2)	1.02±0.29	1.12±0.17	<0.001**
LS-spine BMD (kg/m^2)	0.93±0.23	0.99±0.12	<0.001**

**P - Highly significant. SD: Standard deviation, BMD: Bone mineral density, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LS: Lumbo-sacral

Table 3: Comparison of bone mineral densities of cases and controls according to gender and age

BMD	Groups	Mean±SD				
		Gender		Age (years)		
		Male (*n*=124)	Female (*n*=76)	<40 (*n*=32)	40-60 (*n*=112)	>60 (*n*=56)
Whole body	Case	1.08±0.18	0.92±0.18	1.09±0.20	0.99±0.14	0.83±0.21
	Control	1.17±0.17	1.03±0.19	1.31±0.15	1.13±0.17	1.02±1.11
	P	<0.001**	<0.001**	<0.001**	<0.001**	<0.001**
Hip	Case	1.08±0.15	0.95±0.28	1.19±0.34	1.04±0.22	0.90±0.34
	Control	1.24±0.17	1.13±0.26	1.31±0.14	1.11±0.15	1.02±0.12
	P	<0.001**	<0.001**	NS	NS	NS
LS spine	Case	0.98±0.12	0.95±0.66	1.06±0.21	0.94±0.24	0.85±0.18
	Control	1.40±1.01	1.04±0.25	1.06±0.12	1.01±0.11	0.95±0.12
	P	<0.001**	<0.001**	NS	NS	<0.05*

*P: statistically significant, **P: Highly significant. BMD: Bone mineral density, SD: Standard deviation, NS: Nonsignificant, LS: Lumbo-sacral

Association of independent variables with hepatic osteodystrophy among chronic liver diseases cases

The descriptive statistics of CLD cases about HOD are shown in Table 4. The overall prevalence of HOD among the cases was 70%, whereas 34% of patients were diagnosed with osteopenia and 36% of patients diagnosed with osteoporosis. Male patients were more likely to suffer from HOD ($P < 0.001$). The patients with HOD tended to have greater age ($P < 0.05$), higher bilirubin levels ($P < 0.001$), lower Vitamin D levels ($P < 0.001$), and lower albumin levels ($P < 0.001$). The patients with NASH etiology ($P < 0.05$) and decompensated liver functions (CTP Grading B and C) ($P < 0.05$) significantly tended to have HOD as shown in Table 4.

Influential factors for Hepatic osteodystrophy in chronic liver diseases patients

The association between HOD and factors included in the study was analyzed using conditional logistic regression analysis, as shown in Table 5. The value of R^2 (0.439) showed that the whole model explained 43.9% of the variance in HOD. The most evident result was that patients having decompensated liver function (CTP Grading B and C) and low serum Vitamin D levels had a significantly greater risk of HOD, though the odds of developing HOD in these factors were around 8 times and 18 times, respectively. The other common significant variables in cases were older age (OR = 3.031; $P < 0.05$) and male gender (OR = 3.546; $P < 0.01$). In addition, patients having CLD for more than 5 years (OR = 3.899; $P < 0.05$) were more often to suffer from HOD. Similarly, conditional logistic regression analysis was conducted for osteoporosis at LS-spine and hip in CLD patients, which revealed no influential variables, while in the control group, results showed that low serum Vitamin D level was the only predictor for osteoporosis (OR = 3.672, 95% CI = 1.019–11.902, $P < 0.05$).

Discussion

This case–control cross-sectional survey evaluated the magnitude of HOD in the cases diagnosed with CLD attending a rural hospital for treatment and care. This study explored about two-thirds of CLD patients having problems in the form of metabolic bone diseases, with osteoporosis being the predominant component. HOD was found to be multifactorial in pathogenesis, which often remains unnoticed until later stages. However, exclusive evaluation of HOD in the present era also has greater clinical significance and might help in bolstering the bone density of CLD patients.

Table 4: Basic characteristics and laboratory parameters of chronic liver disease patients with normal bone mineral density and hepatic osteodystrophy

Variables	Subgroups	Mean±SD; Frequency (%)		*P* (Mann–Whitney *U*-test/ Chi-square test
		Normal BMD (*n*=30)	Hepatic Osteodystrophy (*n*=70; Osteopenia=34 and Osteoporosis=36)	
Age (years)		47.80±12.95	53.97±10.54	<0.05*
Gender	Male	12 (40)	50 (71.4)	<0.001**
	Female	18 (60)	20 (28.6)	
Duration of illness		6.87±3.48	7.31±3.01	NS
Type of (CLD)	ALD (36)	8 (26.6)	28 (40)	<0.05*
	NASH (16)	2 (6.7)	14 (20)	
	Hepatitis B/C (48)	20 (66.7)	28 (40)	
Severity of illness (CTP grading)	A (38)	19 (63.3)	19 (27.1)	<0.05*
	B+C (62)	11 (36.4)	51 (71.9)	
Serum bilirubin (mg/dL)		1.85±0.63	2.76±1.63	<0.05*
Serum albumin (gm/dL)		3.28±0.38	2.85±1.05	<0.05*
Serum Vitamin D (ng/mL)		27.23±9.36	18.93±2.96	<0.05*
AST (U/L)		52.66±13.31	63.14±16.57	NS
ALT (U/L)		85.33±10.26	91.71±18.84	NS

*P: Statistically significant, **P: Highly significant. BMD: Bone mineral density, CTP: Child–Turcot–Pugh score, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SD: Standard deviation, CLD: Chronic liver disease, ALD: Alcoholic liver disease, NASH: Nonalcoholic steatohepatitis, NS: Nonsignificant

Table 5: Conditional logistic regression analysis on correlates of hepatic osteodystrophy among the chronic liver disease patients

Variables	Subgroups	OR	95% CI	*P*
Age	>60 years	3.031	1.045-10.679	0.041*
Gender	Male	3.546	1.356-9.259	0.009*
Duration of illness	(> 5 years)	3.899	1.255-12.114	0.019*
Type of CLD	NASH	1.689	0.243-11.764	0.595
	Hepatitis B/C	2.036	0.182-22.727	0.563
Severity of illness (CTP grading)	Decompensated liver (B+C)	8.282	2.575-26.636	<0.001**
Serum bilirubin (mg/dL)	(Normal ≤1.2 mg/dL)	1		
	Abnormal (>1.2 mg/dL)	2.299	0.836-6.324	0.107
Serum albumin (gm/dL)	Normal (≥3.4 g/dL)	1		
	Abnormal (<3.4 g/dL)	0.342	0.141-1.083	0.067
Serum Vitamin D (ng/mL)	Normal (>20 ng/mL)	1		
	Abnormal (<20 ng/mL)	18.456	1.867-173.982	0.013*
AST (U/L)	Normal (up to 45 U/L)	1		
	Abnormal (>45 U/L)	1.429	0.429-6.893	0.461
ALT (U/L)	Normal (up to 60 U/L)	1		
	Abnormal (>60 U/L)	1.096	0.131-13.560	0.890

*P: Statistically significant, **P: Highly significant. Model parameters for hepatic osteodystrophy: Cox and Snell R^2=0.427, Nagelkerke R^2=0.604. Reference category: Age (≤ 60 years); Gender (female); Duration of illness (≤5 years); Type of CLD (alcoholic liver disease); Severity of illness (CTP-A); S. Bilirubin (normal: ≤1.2 mg/dL); Serum albumin (Normal: ≥3.4 g/dL); Serum Vitamin D (Normal: >20 ng/mL); AST (Normal: up to 45 U/L); ALT (Normal: up to 60 U/L). OR: Odds ratio, CI: Confidence interval, CLD: Chronic liver disease, NASH: Nonalcoholic steatohepatitis, CTP: Child–Pugh–Turcotte, AST: Aspartate aminotransferase, ALT: Alanine transaminase

In the present study, the magnitude of HOD (subnormal T-score, i.e., below − 1 SD) among CLD patients was found to be 70%, suggesting a higher rate, although previous multiple studies conducted all over the globe have also found a similar magnitude of HOD where the observed prevalence rate ranged from 68% to 72% [14,19,26]. In contrast to the present study, a much higher prevalence (80%) was estimated in a study conducted in Portugal [8]. A higher prevalence of HOD (83%–95%) in CLD patients was also reported in a few recent Indian studies [10,15,18]. Such heterogeneity in the observation could be attributed to diversities in the sociocultural background, economic growth of populations, methodology, lifestyles, and food habits. In the present study, around 36% of CLD patients presented with osteoporosis, which is consistent with the prevalence of osteoporosis revealed in multiple studies conducted in the past decade [14,18]. However, a few studies conducted in Turkey [26] and Bangladesh [27] revealed osteoporosis in around 20% and 10% of CLD patients, respectively, which were much lower than the present study. Previously, it was established that HOD eventually causes the degeneration of bone framework particularly trabecular structure or bone configuration resulting in the reduction of BMD and ultimately ameliorates the chances of fragility fracture in

these patients [28]. However, across India, the absolute risk of fragility fractures in CLD patients is not much known might be due to the conduction of a scarce number of surveys that could investigate the accurate incidence of these fractures in CLD cases [15,18]. Furthermore, the studies that display these alterations periodically and estimate their correlation can benefit the researchers in establishing the association between the cause and the effect.

HOD in the CLD patients, even if its development mechanism is not entirely acknowledged, is assumed to be influenced by sociodemographics included in the present study, similar to a study conducted by Hajiabbasi *et al*. [29] and Gatta *et al.* [30] In the conditional logistic analysis, elderly patients (>60 years) had more than three times the higher odd risk of low bone mass when compared with younger CLD patients. Consistent with the present study, an observational study in China done by Zheng *et al*. [19] also found that HOD was around two times more likely in older patients, and age was one of the paramount predictors for HOD [20]. As stated earlier in the literature, HOD could be disastrous in older patients with CLD [31]. In incongruence with the observations of this survey, a few authors from India [18] and Turkey [26] explained the statistically insignificant association between the age factor and HOD. In the present survey, it was also revealed that male patients with CLD exhibited more than three times higher odds of risk of HOD as compared to their female counterparts, incongruent to the findings observed by Zheng *et al*. [19], in which female patients had three times higher odd propensity for developing HOD. Another dissimilar outcome was revealed in a study carried out by Savic *et al.* [32], in which a statistically significant relationship between low bone mass and male gender could not be determined. Previous literature has conflicting interpretations on this matter. Ehnert *et al.* [33] revealed that female patients were highly prone to bone mass loss. However, the available literature from the Indian subcontinent has not established any correlation between HOD and gender [10,18]. As one-third of cases included in the present study were affected by ALD and most of them were male, it could well be the possible explanation for this factor being a risk for the development of HOD. The present study evaluated the significant association between HOD and duration of illness where odds increased around four times, which is in concordance with a study done in China on 4000 patients [34]. Ehnert *et al.* [33] also evaluated a positive correlation of HOD with the duration of illness. These findings can be regarded as preliminary in the Indian context, as previous data, particularly focusing on the effects of the duration of CLD on BMD, are very limited. Therefore, screening of HOD by DEXA scanning should be initiated at an early age in patients with CLD, which might be the key to preventing the risk of fractures in CLD patients to improve morbidity and quality of life.

In the analysis of peculiar etiologies of hepatic disease in the present study, none of the etiologies were established as an influential variable for HOD. These findings were assonance with other findings revealed by a few studies conducted across India [10,15,35]. In concordance with the present study, a recent meta-analysis of five cross-sectional studies also observed that NASH did not show a significant association with HOD [36]. In dissonance with the results of the present survey, a few surveys showed a high risk of low BMD in hepatitis C patients [37], hepatitis B patients [38], and patients with NASH etiology [12]. Interestingly, patients with decompensated liver function (CTP Grading B and C) had eight times higher odds of risk of developing HOD than the patients with CTP-A in the present survey. It was found that osteoblasts' activity and the number have been decreased due to the release of cytokines, and impaired bone remodeling due to hormone secretion might be the reason for the higher risk of HOD in patients with higher CTP gradings [5,7]. In assonance of this finding, a few studies also observed that the severity of liver dysfunctions measured by CTP grading is correlated with HOD where the chances of BMD to become low have been increased as the severity progresses [8,29,35]. Although there is an extensive literature available confirming the relationship between low BMD and the CTP grading, contradictory observations prevail. However, a few studies showed no correlation between the severity of illness and HOD [19,26]. Even previous Indian studies have also shown no correlation between the same [18,39]. The reason for this discrepancy could be because most of the studies enrolled patients with only CTP-B and C gradings, whereas the present study enrolled patients from Class A as well. The present study explained the statistically insignificant association between HOD and studied laboratory parameters except for the level of serum Vitamin D. It was revealed that the propensity of HOD increased more than 18 times CLD cases who had a lower level of serum Vitamin D level than their counterparts and was identified as the strongest influential factor for HOD among studied parameters in the present study. The probable intrinsic mechanisms for this include decreased hepatic hydroxylation of Vitamin D and decreased plasma binding proteins, which leads to increased resorption of bone and decreased resorption of calcium, resulting in bone loss and decreased bone formation [40]. Similarly, a few studies conducted in the Indian context confirmed that lower level of serum Vitamin D levels is a significant independent, influential variable for HOD [10,18], while other studies raised controversy with varying findings for the nonsignificant association between the same [26,41]. De *et al.* [18] and Garg *et al*. [39] suggested that an increase in serum parathormone (PTH) levels is the main determinant of bone health for any given value of serum Vitamin D, and caution must be taken in investigating the correlation between HOD and low level of serum Vitamin D. Counseling regarding supplementation with calcium- and Vitamin D-enriched food (if deemed insufficient) is usually recommended to prevent further loss of bone mass in CLD cases, although their efficacy is still inconclusive [7].

The present survey is one of the few from rural India which have investigated a series of influential variables for HOD that might be different from the profile of influential factors revealed in the studies conducted in urban and developed countries, which is the main strength of the present case–control study. Second, a stratified subgroup comparison of bone mass density values between the CLD and non-CLD cases was done. Third, in this survey, a standard definition

for the classification of CLD was used along with an updated review of HOD risk factors. Finally, the details regarding the usage of drugs certainly affecting bone mass were also collected.

This case–control study designed at a single center is fraught with a few limitations like the unable to establish a temporal association between the influential variables and outcome. Hence, it would be necessary to conduct randomized, prospective, multicenter studies on a larger homogeneous group with CLD with specific etiologies in their numerous phases. Furthermore, control selection should be at the community level, which might not have been adequately addressed in the present study design. Second, the present study lacks data on other factors affecting BMD in these patients such as metabolic parameters, BMI, amount of nutrition intake, level of PTH and calcium, and other markers of bone turn because of logistic and cost restraints. Third, researchers were well known to the case and control status of the patients which might have produced the information bias in the present survey. Finally, it was observed that the mean values of some parameters were quite close to the upper normal limit. It means that some of the abnormal liver testing controls were not healthy controls.

Conclusions and Future Suggestions

The findings of the present survey revealed that a greater proportion of CLD patients in a rural setting experienced HOD. It was also evaluated that progression of HOD correlates with a longer duration of illness and more severity. In addition, elderly subjects may require to be screened for low BMD in our rural communities. This study buttresses the need for prescribing calcium and Vitamin D in CLD cases and the generation of additional information on it. Furthermore, incoming studies should focus on measures to inverse these influential variables, which might bring a paradigm shift in decreasing the mortality rate and in ameliorating their quality of life.

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Conflicts of interest

There are no conflicts of interest.

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