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Frequency of Vitamin D Deficiency in Cirrhotic Versus Non-Cirrhotic Liver Disease Patients

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ABSTRACT

OBJECTIVE: To compare the frequency of vitamin D levels between cirrhotic and non-cirrhotic liver disease patients.
METHODOLOGY: This retrospective comparative cross-sectional study compressed 296 diagnosed chronic liver disease patients who visited the Department of Gastroenterology at the Aga Khan University Hospital in Karachi, fulfilling the study inclusion criteria. Demographic and clinical characteristics such as age, sex, disease duration, etiology and severity of all patients were obtained. Cirrhotic status and vitamin D levels were noted.
RESULTS: The mean age was 41.48+/-9.88 years, and the mean vitamin D level in chronic liver disease patients was 14.61+/-8.37 (ng/ml). In cirrhosis and non-cirrhosis patients, mean vitamin D levels were (12.97 vs 16.08; P: 0.001), respectively. Significantly reduced levels were observed in Cirrhotic patients. In cirrhotic patients, vitamin D deficiency was more prevalent than the non-cirrhotic group (80.7% vs 66%; P: 0.004); overall, 73% of chronic liver disease patients were diagnosed as vitamin D deficient.
CONCLUSION: In chronic liver disease patients, liver cirrhosis increases the likelihood of vitamin D deficiency. Factors like young age, male sex, and etiology (hepatitis C virus) strongly correlate with vitamin D deficiency. Furthermore, patients with advanced liver disease are more prone to be vitamin D deficient.

KEYWORDS: Vitamin D deficiency, chronic liver disease, Chirrhotic Liver disease

INTRODUCTION

Chronic liver disease (CLD) is one of the leading contributors to morbidity and mortality across the world. It is responsible for more than one million annual deaths; it accounts for about 3.5% of all worldwide deaths with a global rank of 11th, while in South Asia, it stands at 10th spot [1,2]. Liver cirrhosis has become the 4th most common cause of mortality in many countries, and it has had a significant negative impact on public health worldwide. The main contributor to liver cirrhosis is the Hepatitis C virus (HCV). Other than that, chronic hepatitis B infection, alcohol, non-alcoholic steatosis hepatitis, cholestatic disorders, and autoimmune conditions are also etiological factors[3].

Vitamin D has two forms: Ergocalciferol (Vit-D_2) & Cholecalciferol (Vit-D_3), which are present in the human body as an essential fat-soluble vitamin. The kidneys are where vitamin D is ultimately hydroxylated to become active. Developed countries have a prevalence of approximately 20%, and low socioeconomic countries have up to 100%. Deficiency of vitamin D affects several pathophysiology mechanisms in the human body[4]. Vitamin D deficiency affects more than 30% of CLD patients[5]. Low vitamin D levels seem widespread in healthy controls and more prevalent in people with chronic illnesses. The optimized vitamin D level for those with CLD is yet undetermined[6].

Several investigations have demonstrated that CLD and its severity are highly connected with inadequate levels of vitamin D. The incidence reported in cirrhotic patients is 64-92%, which is considerably higher than that of healthy subjects due to insufficient sun exposure and malnutrition. CLD patients receive less vitamin D from food sources. Further, Low amounts of active hormones are caused by inadequate hydroxylation of vitamin D, which also increases the vitamin's catabolism [7, 8]. Age, sex, Child Turcotte Pugh (CTP) class and end-stage liver disease score model are all associated with vitamin D deficiency [3]. According to previous studies, vitamin D levels fall as liver disease worsens. Patients with liver cirrhosis and healthy individuals may benefit from having their vitamin D levels monitored and managed [3, 9].

Low vitamin D levels are commonly observed in the general population and are more common in those with chronic conditions. The optimized Vitamin D levels for those with CLD are yet undetermined [6, 10]. Vitamin D has been associated with CLD, and various types of liver disorders have been demonstrated to indicate vitamin D deficiency often. Recent studies have shown that patients with CLD had a higher incidence of insufficient vitamin D levels than the general population. Moreover, it has been stated that vitamin D insufficiency increases as liver disease worsens. It is crucial to the normal progression of CLD like HCV and Non-alcoholic fatty liver disease (NAFLD)[11, 12].

Even though vitamin D deficiency is a prevalent problem in CLD patients, there is a lack of information on its prevalence and its relation with disease severity that has been examined and compared across different degrees of CLD severity, particularly in subtropical, middle, and low-income countries. By being informed about this, general practitioners and gastroenterologists could identify vitamin D deficiency in the CLD population early and establish treatment goals in patients with such diseases to minimize its damaging effects over time. This research compared the vitamin D levels in CLD patients with and without cirrhosis.

METHODOLOGY

This Retrospective comparative cross-sectional study was performed at the Department of Gastroenterology Aga Khan University Hospital, Karachi, from January to December 2022. Data from all the CLD patients who visited the hospital and fulfilled the selection criteria were obtained for the study. The estimated sample size was 296, according to the WHO sample size calculator, considering the vitamin D deficiency prevalence in cirrhotic patients 34.4% [3] at a Confidence level of 95% and **6% Margin of error**.

Diagnosis of CLD was defined as any of the following diseases lasting more than six months. Hepatitis B and Hepatitis C were confirmed by serological markers Hepatitis B surface antigen (HepB sAg) and anti hepatitis-C virus antibodies (Anti HCV Ab) by ELISA (enzyme-linked immunosorbent assay). NAFLD was confirmed by clinical history and ultrasound. Findings showing: (1) increased echogenicity of liver parenchyma assessed by liver-kidney contrast, (2) decreased clarity of the borders of intrahepatic vessels, and (3) decreased penetration of ultrasound signal and visibility of diaphragm."

Patients aged between 25-75 years of either gender were included. Patients who were taking steroids or supplementations of vitamin D or calcium, patients with gastric bypass, celiac disease, malabsorption syndrome, chronic kidney disease (CKD), cholestatic liver disease, inflammatory bowel, tuberculosis, and hepatocellular carcinoma (HCC) or other malignancies were excluded.

Demographic and clinical characteristics such as age, gender, etiology, and disease duration were reported. CLD patients were divided into cirrhotic and non-cirrhotic groups. Cirrhosis was defined based on any three or more of the following findings on the abdominal ultrasound: (1) Reduced liver size; longitudinal diameter less than 90mm of the right and 70mm of the left lobes, (2) Nodularity of liver surface, (3) Coarsening of liver echo texture and (4) Portal hypertension (enlarged portal vein size >13mm) labeled as cirrhotic. Child Turcotte Pugh CTP class was calculated for all cirrhotic patients. Rests of the patients were labeled as non-cirrhotic CLD patients. Vitamin D status was noted after measuring the serum concentration of 25-hydroxyvitamin D. For that, a 5 ml venous blood sample of each CLD patient was taken and sent to the hospital laboratory. Vitamin D analysis was performed using an automated chemiluminescence immunoassay (DiaSorin LIAISON) with a laboratory. A cutoff value < 20 ng/mL was labeled as a deficiency.

Data was analyzed on "Statistical Package for Social Sciences (SPSS)" Version 22. Frequency(%) for categorical variables and quantitative variables Mean±SD were calculated. Post-stratification analysis was performed on age, gender, Cirrhosis status, etiology, Child Turcotte Pugh CTP class, and disease duration to see these factors' impact on study outcomes. The chi-square test and t-test were used. The significance level is set at 0.05.

RESULTS

Out of the total 296 patients, 140(47.3%) patients were cirrhotic. The average age of patients was 41.48±9.88 years, the mean disease duration was 15.88±5.07 months, and the mean vitamin D level was 14.61±8.37ng/ml. Mean vitamin D levels in patients with cirrhosis vs. without cirrhosis had statistically significant results (12.97 vs. 16.08; P: 0.001).

Among CLD patients, 121 (86.4%) were aged 50 or less in the cirrhotic group and 142 (91%) in the non-cirrhotic group. There were 77(55%) male patients in the cirrhotic group and 84(53.8%) male patients in the non-cirrhotic group. Most of the patients' disease duration was reported to be more than 12 months in cirrhotic group 101(72.1%) and in non-cirrhotic group 104(66.7%) patients.

Most common etiologies among the disease patients were HCV 155(52.3%), 118(39.9%) while Alcoholic liver disease only reported in 18(6.1%) and 5(1.7%) patients had NAFLD.

Vitamin D deficiency is found in 73% of CLD patients. Vitamin D deficiency was more prevalent in cirrhotic patients than in the non-cirrhotic group (80.7% vs. 66%; P: 0.004). (**Table I**)

Most of the cirrhotic patients had Child-Pugh Class C 69(49%), 52(37%) patients had Class A, and 19(14%) had Class B.

The findings of the stratified analysis showed that patients aged 50 years or less, male gender, disease duration less than 12 months, and HCV were significantly associated factors ($P<0.05$). Among the Cirrhotic patients with the following characteristics, the prevalence of Vitamin D deficiency is comparatively high compared to non-cirrhotic patients. (**Table II**)

The association of vitamin D deficiency was compared with CTP Class in cirrhotic patients. Among all the cirrhotic patients, a high prevalence of vitamin D deficiency was reported without any significant difference (P-value: 0.490). Still, notably, patients with CTP Class "B" and "C" had relatively higher deficiency as compared to Class A cirrhotic patient.

Vitamin D levels were also compared with cirrhosis status regarding the associated factors. (**Table III**)

Table I: Demographic and clinical characteristics of Cirrhotic and Non-Cirrhotic Liver disease patients

Patient's Characteristics	Cirrhotic	Non-Cirrhotic	Total	P-values
Age (in years)	41.66+/-10.81	41.31+/-9.01	41.48+/-9.88	**0.762**
Duration of Disease (in months)	16.01+/-5.05	15.77+/-5.09	15.88+/-5.07	**0.688**
Vitamin D level ng/mL	12.97+/-7.64	16.08+/-8.73	14.61+/-8.37	**0.001**
Age groups (in years)				**0.21**
50 or less	121(86.4%)	142(91%)	263(88.9%)	
More than 50	19(13.6%)	14(9%)	33(11.1%)	
Gender				**0.842**
Female	63(45%)	72(46.2%)	135(45.6%)	
Male	77(55%)	84(53.8%)	161(54.4%)	
Duration of Disease (in months)				**0.308**
12 or less	39(27.9%)	52(33.3%)	91(30.7%)	
More than 12	101(72.1%)	104(66.7%)	205(69.3%)	
Etiology				**0.927**
Alcoholic liver disease	8(5.7%)	10(6.4%)	18(6.1%)	
Hepatitis B	54(38.6%)	64(41%)	118(39.9%)	
Hepatitis C	76(54.3%)	79(50.6%)	155(52.3%)	
NAFLD	2(1.4%)	2(1.3%)	5(1.7%)	
Vitamin D deficiency				**0.004**
No	27(19.3%)	53(34%)	80(27%)	
Yes	113(80.7%)	103(66%)	216(73%)	

Mean+/-SD; n (%); Independent t-test; Chi square test; P-value<0.05.

Table II: Association between Cirrhosis and Vitamin D deficiency in Liver disease patients

Associated Factors		Vitamin D deficiency	Cirrhotic	Non Cirrhotic	Total	P-values
Age groups	50 or less	No	23(19%)	48(33.8%)	71(27%)	**0.007**
		Yes	98(81%)	94(66.2%)	192(73%)	
	More than 50	No	4(21.1%)	5(35.7%)	9(27.3%)	**0.35**
		Yes	15(78.9%)	9(64.3%)	24(72.7%)	
Gender	Female	No	9(14.3%)	16(22.2%)	25(18.5%)	**0.272**
		Yes	54(85.7%)	56(77.8%)	110(81.5%)	
	Male	No	18(23.4%)	37(44%)	55(34.2%)	**0.008**
		Yes	59(76.6%)	47(56%)	106(65.8%)	
Duration of disease	12 or less	No	6(15.4%)	20(38.5%)	26(28.6%)	**0.02**
		Yes	33(84.6%)	32(61.5%)	65(71.4%)	
	More than 12	No	21(20.8%)	33(31.7%)	54(26.3%)	**0.083**
		Yes	80(79.2%)	71(68.3%)	151(73.7%)	
Etiology	Alcoholic liver disease	No	3(37.5%)	4(40%)	7(38.9%)	**0.914**
		Yes	5(62.5%)	6(60%)	11(61.1%)	
	Hepatitis B	No	10(18.5%)	21(32.8%)	31(26.3%)	**0.079**
		Yes	44(81.5%)	43(67.2%)	87(73.7%)	
	Hepatitis C	No	14(18.4%)	26(32.9%)	40(25.8%)	**0.039**
		Yes	62(81.6%)	53(67.1%)	115(74.2%)	
	NAFLD	No	0(0%)	2(66.7%)	2(40%)	**0.136**
		Yes	2(100%)	1(33.3%)	3(60%)	

n(%); Chi square test; P-value<0.05.

Figure I: Association of Vitamin D Deficiency with Child-Pugh Class in Cirrhotic Patients

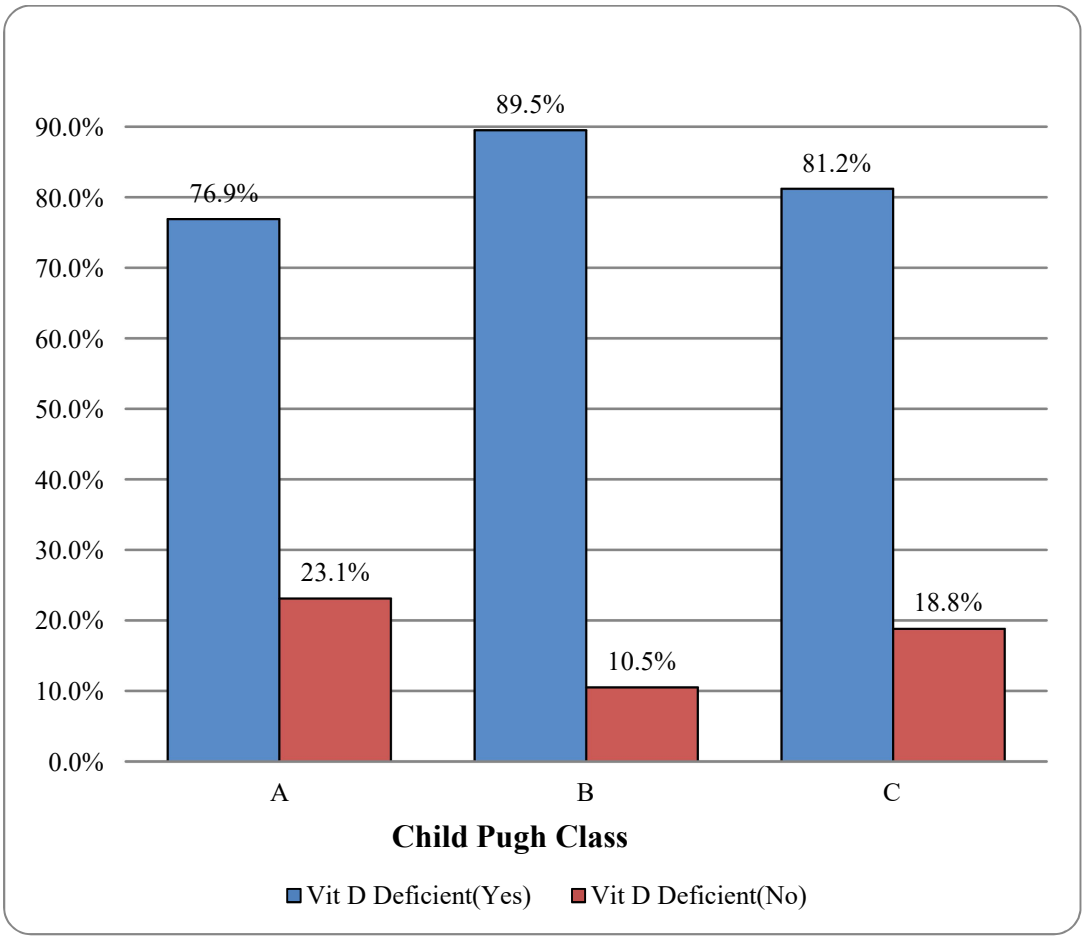

Table III: Comparison between Cirrhosis status and mean Vitamin D level in Liver disease patients

Associated factors	Vitamin D level (Mean+/- SD)		P-values
	Cirrhotic	Non-Cirrhotic	
Age groups (in years)			
50 or less	12.90+/-7.6	16.02+/-8.80	**0.003**
More than 50	13.40+/-8.15	16.71+/-8.25	**0.259**
Gender			
Female	13.84+/-7.51	15.47+/-7.68	**0.216**
Male	12.26+/-7.73	16.60+/-9.56	**0.002**
Duration of Disease (in months)			
12 or less	13.02+/-7.64	16.22+/-8.49	**0.066**
More than 12	12.95+/-7.69	16.01+/-8.89	**0.009**
Etiology			
Alcoholic liver disease	15.49+/-9.21	14.81+/-10.53	**0.888**
Hepatitis B	14.45+/-7.76	17.03+/-8.74	**0.097**
Hepatitis C	11.64+/-7.33	15.28+/-8.35	**0.005**
Non Alcoholic Fatty liver disease	13.15+/-1.63	21.20+/-13.62	**0.487**
Child-Pugh Class			
A	12.90+/-8.29	---	**0.698**
B	11.69+/-6.30	---	
C	13.37+/-7.53	---	

Mean+/-SD; Independent t-test; P-value<0.05. ANOVA test for Child-Pugh Class.

DISCUSSION

Vitamin D deficiency is correlated with CLD and has also been shown to be a frequent finding in different liver diseases[6]. This study compared the vitamin D levels with and without cirrhosis in CLD patients. The most significant finding from earlier research was that vitamin D deficiency in patients with non-cirrhotic liver disease appeared to be caused by underlying liver diseases, such as NAFLD, alcoholic liver disease, and hepatotropic viruses[8,10]. Furthermore, the overall survival of cirrhotic patients is negatively influenced by vitamin D insufficiency, which has been connected to active HCC[11].

According to the current research, 73% of CLD patients had vitamin D deficiency, which is relatively high compared to previous literature. **Arteh et al.**[12] showed that 92% of individuals with CLD had a significant frequency of vitamin D deficiency, with at least 1/3rd having severe deficiency. These levels should be examined, and replenishment should be administered to cirrhotic patients. **Zhao XY et al.**[13] stated that Vitamin D deficiency impacts 1/3rd of liver cirrhotic patients, and in certain CLD patients, it causes hepatic osteodystrophy. The study showed Vitamin D levels as 14.6±8.4 ng/ml. This level is below the normal range.

The critical component in vitamin D deficiency caused by liver cirrhosis is the suppression of Vit-D hydroxylation, even though the reasons for the deficiency in cirrhotic patients are multifactorial. The study showed Vit-D levels as 14.61±8.37 ng/mL. This level is below the normal range. Furthermore, in another study, mean vitamin D levels were 23.2 vs. 34.1 ng/mL in CLD patients and healthy controls. The author suggested that many CLD patients have low vitamin D levels, which might contribute to various musculoskeletal symptoms. In 34% of patients, low levels of vitamin- D were discovered[3].

Due to vitamin D's anti-fibrotic properties and its impact on the immune system, it is essential in CLD physiopathology. HCV patients are more prone to deficient vitamin D levels (46% to 92%), and more than 25% have severe deficiency [14, 15]. In the current research, cirrhotic with HCV have an elevated risk of reduced vitamin D levels compared to non-cirrhotic CLD patients (81.6 vs. 67.1%). It also relates to CKD, multiple sclerosis, psoriasis, and OA[15,16]. **Hamid S et al.**[17] showed that 78% of HCV patients were vitamin D deficient. Among them, 54% of non-cirrhotic patients and 100% of cirrhotic patients were deficient in vitamin D. There might be several treatment implementations in case of a connection between CLD and vitamin D deficiency. The relation between vitamin D deficiency and the degree of fibrosis, viral etiology, co-morbidities, and liver function may support its utility as a prognostic indicator and diagnostic tool[6].

Memon S et al.[18] exhibited that 55% of CLD patients were males; 71% had vitamin D deficiency. In our study, 81.5% of female and 65.8% of male CLD patients suffered from vitamin D deficiency. In contrast with current findings, the younger age strongly relates to vitamin D deficiency ($P< 0.05$). Numerous in-depth analyses were conducted to demonstrate lower vitamin D status in patients with cirrhosis, and a study done by **Zhao et al.**[19] explored that cirrhotic patients had significantly low vitamin D levels. Compared to our study, **Kumar et al.**[9] found that only 12% of cirrhotic patients had adequate levels, while 88% had deficient levels. These collective researches support our findings, which show that people with CLD have vitamin D deficiency.

Similar to the current study finding, **Ahmed et al.**[20] also reported that almost half of the cirrhotic population had Child-Pugh Class C, followed by Class A and Class B. Our study findings discovered that most patients with liver cirrhosis were vitamin D deficient. Among them, more than 80% of patients had advanced CTP classes B and C and 77% of patients with CTP class A

had vitamin D deficiency. In our study, male sex, younger age, and advanced CTP classes are all significantly associated with deficient vitamin D levels. Patients with CTP classes B or C must be monitored regularly for their vitamin D levels, and this deficiency has to be treated to enhance the patient's overall health[3]. In advanced Child stages, vitamin D levels gradually decrease. Low vitamin D in cirrhotic patients may be a helpful indicator of mortality. Furthermore, there is a significant tendency for vitamin D levels to predict mortality in people with cirrhosis, and a cutoff of 10 ng/ml appears to identify people who are more likely to die. Additionally, vitamin D is a reliable indicator of liver disease and an excellent synthesis-related measure[21].

Malham et al.[5] also emphasized the need for vitamin D monitoring in all CLD patients, particularly cirrhotic patients. They stated the usefulness of therapy in hepatic insufficiency-related bone disease. **Garcia-Alvarez et al.** [22] also suggested HCV patients get their vitamin D levels monitored.

The study's strength is that it not only brings attention to vitamin D deficiency that affects a substantial number of CLD patients but also evaluates the vitamin D deficiency in CLD patients with cirrhosis. It makes it a more focused yet comparable research equally valuable to primary healthcare providers and liver specialists. Additionally, it highlights the importance of routine laboratory examinations for patients, particularly those with severe CLD, because of the frequently observed adverse effects. In Pakistan, a subtropical country with abundant sun exposure, baseline vitamin D levels are expected to remain normal or rise. We could examine the variation in extreme ages owing to patients included in the research. The considerably large sample size used in this study is an additional strength. Our study was limited because it was only carried out at one tertiary care facility using a retrospective record review to gather sample data. As a result, verification of the results' generalization is needed. More extensive cohort studies in different populations would validate these results.

CONCLUSION

Vitamin D deficiency is more likely to affect CLD patients with liver cirrhosis. Young age, male sex, etiology, and the advanced Child-Pugh class of liver cirrhosis have been identified as significantly associated factors for vitamin D deficiency. Patients with CTP Class B and C should frequently have their vitamin D levels evaluated, and the deficiency has to be treated right once to enhance the overall health of cirrhotic patients. Furthermore, when the Child-Pugh Class advances, serum vitamin D concentration decreases. A predictive criterion for liver cirrhosis severity might be the increasing deficiency of vitamin D since it was associated with the severity of CLD. Also, it might be related to a higher likelihood of morbidity and mortality. Therefore, Vitamin D level screening should be done in all chronic liver disease patients, especially with cirrhosis. Vitamin D supplementation should be given irrespective of the presence of bone diseases. Prospective cohort studies with larger sample sizes and randomized trials need to be conducted to better assess the role of vitamin D as a diagnostic tool and prognostic index for determining disease severity in CLD patients.

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Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publically. The questionnaire used in this is given in the Annexure.

AUTHOR CONTRIBUTION

Haroon AL: Study Design, data collection, statistical analysis, manuscript writing and is responsible for the integrity of research and final approval of manuscript
Haroon AN: Conception and design, manuscript writing and revised it critically for important intellectual content
Sohail Z: Data collection, manuscript writing and article review.
Nizami RA: Data collection, manuscript writing and article review.
Kumar A: Data collection, manuscript writing and article review.

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