Original Article

Vitamin D Deficiency and Its Relationship with Child-Pugh Class in Patients with Chronic Liver Disease

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Abstract

Background and Aims: Skeletal manifestation in liver diseases represents the minimally scrutinized part of the disease spectrum. Vitamin D deficiency has a central role in developing hepatic osteodystrophy in patients with chronic liver disease. This study aimed to investigate vitamin D levels and their relationship with disease advancement in these patients. ***Methods:*** Vitamin D levels were checked in 125 chronic liver disease patients. The patients were classified in three stages according to Child-Pugh score: A, B and C. The relationship of vitamin D levels with Child-Pugh score and other variables in the study was assessed by the contingency coefficient. Correlation and logistic regression analyses were also carried out to find additional predictors of low vitamin D levels. ***Results:*** Among the patients, 88% had either insufficient or deficient stores of vitamin D, while only 12% had sufficient vitamin D levels (p >0.05). Vitamin D levels were notably related to Child-Pugh class (contingency coefficient = 0.5, p <0.05). On univariate and multinomial regression analyses, age, female sex, MELD and Child-Pugh class were predictors of low vitamin D levels. Age, model of end-stage liver disease score and Child-Pugh score were negatively correlated to vitamin D levels (p <0.05). ***Conclusions:*** Vitamin D deficiency is notably related to age, female sex and model of end-stage liver disease score, in addition to Child-Pugh class of liver cirrhosis. Vitamin D levels should be routinely checked in patients with advanced liver cirrhosis (Child-Pugh class B and C) and this deficiency must be addressed in a timely manner to improve general well-being of cirrhotic patients.

Citation of this article: Jamil Z, Arif S, Khan A, Durrani AA, Yaqoob N. Vitamin D deficiency and its relationship with Child-Pugh class in patients with chronic liver disease. J Clin Transl Hepatol 2018;6(2):135–140. doi: 10.14218/JCTH.2017.00055.

Introduction

Liver cirrhosis has exerted a major burden on public health globally, being the 4th leading cause of death in many countries.[1] It is estimated that around one million deaths are attributed to liver cirrhosis each year.[2] The foremost cause of liver cirrhosis in many countries of the world is chronic hepatitis C virus infection.[3] Many other etiological agents, such as chronic hepatitis B infection, nonalcoholic steatotic hepatitis, alcohol, cholestatic disorders, chronic vascular obstructive diseases and autoimmune diseases, also result in liver cirrhosis.[1,3]

The Child-Pugh (CP) score is a widely used scoring system to predict the 1-year survival rate among cirrhotic patients. First described by Child and Turcotte and later modified by Pugh *et al.*,[4] this score uses five parameters (hepatic encephalopathy, prothrombin time (PT), ascites, serum bilirubin and serum albumin) to classify the patients in early, intermediate and advanced stages of liver cirrhosis. Esophageal varices, ascites, portal hypertension, hepatic encephalopathy and hepatocellular carcinoma are all well studied and well-known complications of liver cirrhosis.[5] A less studied complication of liver cirrhosis, however, is represented by its skeletal manifestations.

Liver cirrhosis forms a complex relationship between serum calcium, phosphate, parathyroid hormone and vitamin D levels, affecting the musculoskeletal system. These skeletal manifestations in liver disease are termed hepatic osteodystrophy. Hepatic osteodystrophy results in a high risk of fractures in cirrhotic patients, thus negatively affecting their morbidity.[6,7] Vitamin D deficiency plays a key role in development of hepatic osteodystrophy.[7] Fish, eggs and oral supplements are dietary sources of vitamin D (fat soluble vitamin); however, the major source is sun exposure of the skin. Pro-vitamin D_3 (cholecalciferol), whether obtained from diet or sunlight, remains stored in fat cells until the first step of hydroxylation takes place in the liver, resulting in the synthesis of 25-hydroxy cholecalciferol. 1,25-dihydroxy cholecalciferol (active vitamin D) is synthesized in the kidneys by the final step of hydroxylation.[8]

Vitamin D is necessary for functions and health of both muscles and bones in our body. In addition, vitamin D has many extra skeletal functions. Many chronic diseases, like diabetes mellitus, chronic infections and malignancy (breast, prostate and colon), are less likely to develop with presence of adequate stores of vitamin D in our body because many cells of the body like hepatocytes, macrophages, immune B and T cells express vitamin D receptors on their surface.[9,10] Patients suffering from chronic liver diseases are mostly vitamin D deficient. It is estimated about one-third of cirrhotic patients have vitamin D deficiency.[6]

There are multiple mechanisms by which vitamin D deficiency occurs in these patients.

1. Cholestasis due to CLD results in malabsorption of fats and fat soluble vitamins (A, D, E, K).[11]

Keywords: Vitamin D deficiency; Liver cirrhosis; Osteodystrophy; Liver disease; Skeletal manifestations.

Abbreviations: CLD, chronic liver disease; CP, Child-Pugh; PT, prothrombin time; INR, international normalized ratio.

Received: 13 August 2017; Revised: 20 October 2017; Accepted: 12 December 2017

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2. Anorexia due to chronic illness resulting in dietary deficiency of vitamin D.[11]
3. Reduced mobility due to chronic illness resulting in limited sun exposure and reduced levels of cholecalciferol.[12]
4. Inhibition of hydroxylation of cholecalciferol in liver diseases results in a reduced synthesis of 25-hydroxy cholecalciferol.[13]

Skeletal manifestations of CLD are a neglected part of the disease spectrum. Yet, they significantly affect the morbidity of patients with liver diseases. The primary aim of this study was to document vitamin D deficiency in patients with liver cirrhosis and to find its relationship with CP class of the liver cirrhosis. Studying the other factors which lead to vitamin D deficiency in these patients was an additional aim of this study.

Methods

A cohort study was conducted in Fauji Foundation Hospital, Rawalpindi, Pakistan from January 2016 to July 2016. Patients were labeled as a case of CLD if they had any one, or more than one, of the following features: biochemical abnormalities suggesting CLD, like deranged liver function tests in the presence of risk factors leading to CLD (duration >3 months); ultrasonographic findings of CLD (surface nodularity, coarse and heterogeneous liver texture and segmental hypertrophy or atrophy);[14] chronic liver parenchymal changes on liver biopsy; medical records suggesting CLD (medications or previous admissions due to hepatic encephalopathy, ascites or variceal bleeding).

Ultimately, 125 patients fulfilling these criteria were selected for this study. Patients had been excluded from the study if: taking medications which can affect the serum vitamin D levels, like vitamin A, calcium and vitamin D supplements, steroids, antiepileptic drugs and bisphosphonates, etc.; suffering from chronic diseases that can impair calcium and vitamin D metabolism, like chronic kidney disease, malabsorption syndrome, tuberculosis, etc.; presence of hepatocellular carcinomas or other malignancies.

Ethical approval was given by the hospital prior to the study's commencement. Informed consent was obtained from the participant patients. A complete demographic profile of patients was noted. Detailed history and complete examination of patients was carried out. The blood samples of patients were taken and sent for complete blood examination, and testing for levels of serum bilirubin, serum albumin, the international normalization ratio (INR) and 25-hydroxyvitamin D. Hepatitis serology for hepatitis C and hepatitis B were also carried out to find the cause of CLD.

Patients were scored according to Child-Pugh classification and classified into three classes: A, B and C. Five parameters were used to give these scores to patients. The parameters were ascites, hepatic encephalopathy, serum bilirubin (mg/dL), INR and serum albumin (g/dL). Each parameter was scored 1, 2 or 3. The minimum score of CP class was 5 and the maximum was 15. Ascites was graded as mild, moderate or severe by performing a transabdominal ultrasound (Famio 5 Ultrasound Machine; Abex Medical System, Toshiba, Japan). Grades of encephalopathy were determined by a physician during examination. Blood (3 mL) was taken in serum bottles for serum albumin and serum bilirubin, and results were obtained by using a chemistry analyzer (Dimensions RxL Max Chemistry Analyzer; Siemens Healthineers Laboratories, USA). Blood (3 mL in a tube containing 3.2% Na-citrate) was used to determine PT, and results were obtained by using the Sysmex CA-500 Coagulation Analyzer (Siemens Healthcare Diagnostics, Japan). INR was calculated manually by using the patient and control PTs.

Those patients without ascites or hepatic encephalopathy, serum bilirubin <2 mg/dL, serum albumin >3.5 g/dL and INR <1.7 were scored as 5 and 6, and they were classified as CP class A. Patients with mild to moderate ascites, grade 1 or grade 2 hepatic encephalopathy, serum bilirubin 2–3 mg/dL, serum albumin 2.8–3.5 g/dL and INR 1.7–2.3 were given a score from 7 to 9, and they were classified as CP class B. Those patients who had massive ascites and grade 3 or grade 4 hepatic encephalopathy, serum bilirubin >3 mg/dL, serum albumin <2.5 g/dL and INR >2.3 were placed in CP class C, as the scores of their parameters were from 10 to 15.

Blood (2 mL) was drawn from patients to check vitamin D (25-hydroxyvitamin D) levels. Levels were checked in serum using the Elecsays Analyzer (Cobas_e_411 Analyzer; Roche Diagnostics, Germany). Deficiency was defined as vitamin D levels <20 ng/mL; between 21 ng/mL to 30 ng/mL was considered insufficient vitamin D and above 31 ng/mL was considered sufficient. The data of 125 patients with CLD were collected. In addition, 100 healthy individuals were taken as controls, being age- and sex-matched to the disease group.

The mean of vitamin D levels in both groups (patients and controls) was tested by student's *t*-test. Quantitative variables were expressed in terms of mean and standard deviation. Frequency and percentage were used for qualitative measures. The *p*-value was calculated by the contingency coefficient to find a relationship of vitamin D levels to CP scores of liver cirrhosis and also with other variables. Both correlation and logistic regression analyses were also carried out to find additional predictors of vitamin D deficiency in the disease group. SPSS version 20 software (USA) was used for analyzing the data.

Results

Most of the patients in the study were females, as the study was conducted in an ex-servicemen beneficiary hospital. Among the 125 patient participants, 115 (92%) were females and only 10 (8%) were males. The minimum age of the patients was 18 years and the maximum was 84 years, with mean age of 56.88 years.

Among the 125 patients, 117 (93.6%) were affected by chronic hepatitis C infection. The second cause of CLD was hepatitis B infection, affecting 6 (4.8%) patients; the remaining 2 (1.6%) patients had seronegative liver disease. Patients were categorized according to CP class to assess the degree of liver dysfunction. Among the 125 patients, 38 (30.4%) had advanced liver disease and were in CP class C, 48 (38.4%) were CP class A, showing early liver cirrhosis, and 39 (31.2%) were CP class B, indicating the intermediate stage of liver cirrhosis.

The distribution of some baseline variables among the study group is shown in Table 1.

The results of the study showed that many patients suffering from cirrhosis of liver had either deficient or insufficient vitamin D levels. Vitamin D levels in these patients (n = 125) were lower than vitamin D levels in the control group, ranging from 23.16 ± 7.94 ng/mL to 6.00–44.00 ng/mL and 34.13 ± 18.34 ng/mL to 9.00–87.00 ng/mL respectively. Although, statistically, this difference was not significant (p >0.05). Patients were categorized into three groups

Table 1. Distribution of variables among the 125 patients with chronic liver disease

	n	Minimum	Maximum	Mean	Standard deviation
Hemoglobin, g/dL	125	7.80	15.60	9.43	2.15
WCC $\times 10^9$ cells/L	125	1.72	20.20	6.22	3.15
Platelets $\times 10^9$/L	125	24.00	475.00	112.86	75.64
Bilirubin, mg/dL	125	0.41	26.02	2.24	2.01
ALT, U/L	125	20.00	302.00	55.53	38.37
ALP, U/L	125	102.00	575.00	218.50	88.68
INR	125	1.00	2.60	1.67	0.46
Albumin, g/dL	125	2.20	4.30	3.53	0.44
CP score	125	5.00	13.00	7.90	2.27
MELD score	125	10.00	32.00	19.56	6.38

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; CP, Child-Pugh; INR, international normalized ratio; MELD, model of end-stage liver disease; WCC, white cell count.

according to vitamin D levels: patients with deficient (<20 ng/mL), insufficient (20–30 ng/mL) and sufficient (>30 ng/mL) Vitamin D levels. The majority of cirrhotic patients (*n* = 66) had insufficient vitamin D levels (patients: 52.8% vs. controls: 27%). Vitamin D deficiency was also common in these cirrhotic patients. Forty-three patients had deficient levels (patients: 34.4% vs. controls: 26%). Sufficient levels of vitamin D were found in only 16 patients with liver cirrhosis (patients: 12.8% vs. controls: 47%). The patients and controls groups are illustrated in a bar chart according to these three categories of vitamin D (Fig. 1).

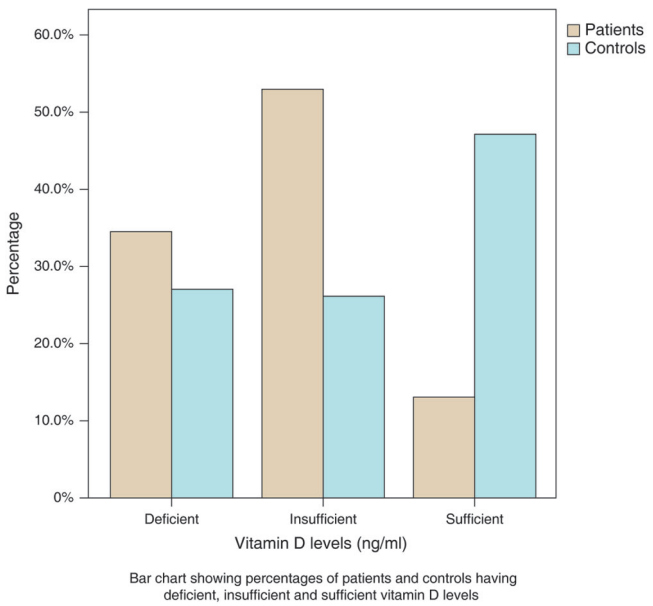

Fig. 1. Patients with chronic liver disease and controls according to vitamin D categories. The X-axis shows the three categories of vitamin D levels: deficiency (<20 ng/mL), insufficiency (20–30 ng/mL) and sufficiency (>30 ng/mL). The Y-axis shows the frequency of patients and controls according to the three categories of vitamin D. The majority of cirrhotic patients (52.8%, *n* = 66; controls: 27%) had insufficient vitamin D levels. Vitamin D deficiency was found in 34.4% (*n* = 43; controls: 26%). Sufficient levels of vitamin D were found in only 12.8% (*n* = 16; controls: 47%) of patients with liver cirrhosis.

The primary aim of this study was to find the association of vitamin D levels with CP class of liver cirrhosis. Although vitamin D levels were not statistically lower than the control group, but vitamin D levels were strongly related to CP classification of liver cirrhosis. Most patients with CP class C were vitamin D-deficient, while none had sufficient vitamin D stores. In contrast to this, 12 patients having CP class A had sufficient vitamin D levels. The results indicated that vitamin D levels in cirrhotic patients are associated with CP classification (p <0.05 and contingency coefficient = 0.5) (Table 2). Thus, as the CP class advances, vitamin D levels decrease (Fig. 2).

The association of vitamin D levels was also studied with different variables, as the secondary aim of the study. The three groups of vitamin D levels showed significant association with age of patients (p = 0.000), serum albumin (p = 0.045), model of end-stage liver disease score (p = 0.003) and CP score (p = 0.000), in addition to the CP class of liver cirrhosis. The association of three categories (deficient, insufficient and sufficient) vitamin D levels with various variables is shown in Table 3. Both regression analysis and correlation analysis were carried out to find the predictors of vitamin D deficiency. In univariate analysis, age, female sex, model for end-stage liver disease score, CP score and CP class (p <0.05) were found to be predictors of vitamin D deficiency.

Multinomial analysis was also carried out. The model-fitting information showed that the model was statistically fit, with chi-square test value of 90.30 and p value of 0.000. The model covered 54% to 63% variation of variables (Cox and Snell pseudo R^2 and Nagelkerke pseudo R^2 respectively) and classified 93.5% of cases. Among quantitative variables age, model for end-stage liver disease score and CP score were found to be predictors of vitamin D deficiency. Female sex and CP class were found to be predictors of low vitamin D levels among qualitative variables. Etiology of liver cirrhosis was not found to be a predictor of low vitamin D levels in our study. Both univariate and multinomial regression analyses of different variables to predict vitamin D deficiency among study group are summarized in Table 4.

Pearson correlation was also carried out to find the relationship of all variables with vitamin D levels. Significant correlation of vitamin D levels was found with age (correlation coefficient = −0.594, p = 0.000), serum albumin (correlation

Table 2. Relationship of vitamin D levels with CP class of cirrhosis of the liver

	CP class			
Categories of vitamin D	A	B	C	*n*
Deficient	7 (14.5%)	7 (17.9%)	29 (76.3%)	43 (34.4%)
Insufficient	29 (60.4%)	28 (71.7%)	9 (23.6%)	66 (52.8%)
Sufficient	12 (25%)	4 (10.2%)	0	16 (12.8%)
n	48	39	38	125

Abbreviation: CP, Child-Pugh.

coefficient = 0.297, p = 0.001), model for end-stage liver disease score (correlation coefficient = −0.452, p = 0.000) and CP score (correlation coefficient = −0.556, p = 0.000).

Discussion

One-third of patients with liver cirrhosis suffer from vitamin D deficiency, and it results in hepatic osteodystrophy in these patients.[6,15] This study aimed to document vitamin D deficiency in CLD patients. Although the cause of vitamin D in cirrhotic patients is multifactorial, the main mechanism through which cirrhosis of the liver causes vitamin D deficiency is the inhibition of vitamin D hydroxylation. Mean vitamin D levels were 23.16 ng/mL (controls: 34.14 ng/mL) in CLD patients according to this study, indicating that many patients with CLD are suffering from insufficient stores of vitamin D, which can be responsible for many musculoskeletal manifestations. Deficient vitamin D stores (<20 ng/mL) were found in 34% of patients. A large number of cirrhotic patients had either deficient or insufficient vitamin D levels; meanwhile, sufficient stores of vitamin D (>30 ng/mL) were found only in 12% of cirrhotic patients.

Many comprehensive studies and trials have been conducted to document vitamin D deficiency among cirrhotic patients. Zhao *et al.*[15] conducted a study on 345 cirrhotic patients and found that vitamin D levels were significantly deficient in these patients. One more study conducted in Spain by Fernandez *et al.*[12] found that among 94 cirrhotic patients 87% had deficient levels of vitamin D. Kumar *et al.*[16] conducted a study on 160 cirrhotic patients and found inadequate levels of vitamin D in 80% of patients. We found that only 12% of patients had sufficient vitamin D levels, while 88% of patients do not have enough stores of vitamin D. These collective studies concur with our results, in that vitamin D is deficient in patients suffering from CLD.

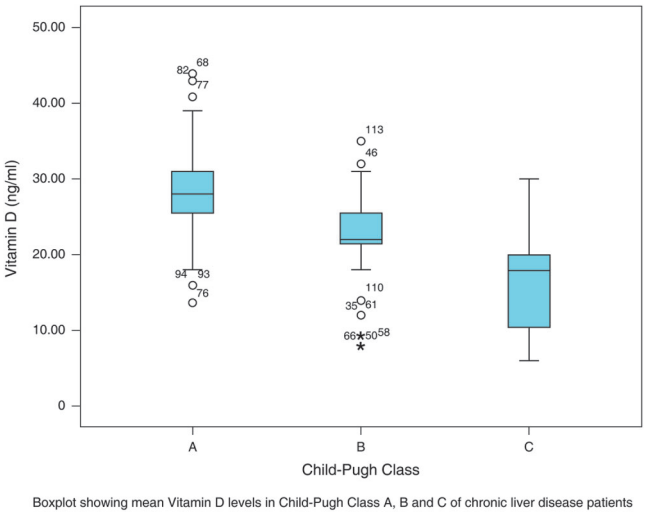

Fig. 2. Vitamin D levels in Child-Pugh class A, B and C for patients with chronic liver disease. Vitamin D levels were much lower in class C, as compared to classes A and B. Vitamin D levels gradually decreased from class A to class C, meaning that as the disease advances the levels decrease further.

The mean vitamin D levels in patients were lower than mean vitamin D levels in the control group, although not significant statistically (p >0.05). The reason is that a deficiency of vitamin D is documented even in the healthy population of many countries. One study conducted by Kiani *et al.*[17] found that 83% patients presenting in the outpatient department with different diseases had deficient levels of vitamin D, with mean levels of 13 ng/dL. One more study conducted by Mehboobali *et al.*[18] on 858 subjects found that 55% of healthy individuals in third world countries have vitamin D deficiency. The causes of vitamin D deficiency in these healthy populations are multifactorial, including dietary, environmental and genetic causes.[17,18] If vitamin D deficiency is already common in such healthy individuals, then how much does cirrhosis of the liver play a role in causing further vitamin D deficiency in such patients belonging to those populations? This question needs to be further studied.

The primary aim was to study the relationship of vitamin D levels with CP class of liver cirrhosis. We found that vitamin D levels were negatively correlated with both model of end-stage liver disease score and CP score, suggesting that as the disease advances vitamin D levels become more deficient (p <0.05). The results of the study are similar to many other studies which have shown that vitamin D level is inversely correlated to the CP score and model of end-stage liver disease score.[19] Two studies conducted by Fernandez *et al.* and Zhao *et al.*[12,15] both found that vitamin D decreases further as cirrhosis of liver advances. Thus, patients with higher scores in the CP classification and model of end-stage liver disease score have notably lower vitamin D levels compared to patients with lower CP and model of end-stage liver disease scores.

Additional predictors of low vitamin D levels were also studied as the secondary aim of this study. Increasing age and female sex were found to be predictors of low vitamin D levels (p = 0.000), in addition to CP class. Junaid *et al.*[20] studied the main reasons of vitamin D deficiency in a healthy population and found that the lack of education regarding a proper fortified diet, limited sun exposure (<30 m) and insufficient use of calcium and vitamin D

Table 3. Distribution of variables among patients with deficient, insufficient and sufficient vitamin D levels

Variable	Deficient, *n* = 43	Insufficient, *n* = 66	Sufficient, *n* = 16	*p**
Age in years	67.71	51.98	49.23	**0.000**
Hemoglobin, g/dL	9.64	9.28	9.48	0.710
WCC $\times 10^3$ cells/L	6.33	6.08	6.47	0.866
Platelets $\times 10^3$ cells/L	94.35	118.47	137.11	0.099
PT, sec	6.02	3.69	2.94	0.076
INR, sec	1.90	1.60	1.40	0.178
Bilirubin, mg/dL	3.03	1.99	1.30	0.268
ALT, U/L	52.73	54.77	65.41	0.506
ALP, U/L	228.69	217.15	198.58	0.494
Albumin, g/L	3.42	3.57	3.65	**0.045**
MELD score	23.19	18.43	14.94	**0.003**
CP score	9.40	7.33	6.41	**0.000**

*Bold font indicates statistically significant values.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; CP, Child-Pugh; INR, international normalized ratio; MELD, model of end-stage liver disease; WCC, white cell count.

supplements in daily life are the main causes of vitamin D deficiency. Female sex, low socioeconomic status, urban residency, smoking and polymorphisms in the sequences encoding vitamin D binding proteins are additional studied risk factors, which contribute to deficiency of vitamin D in the healthy populations of these countries.

We found negative correlation between age and CP scores. As the age and CP score increases, the levels further decrease. These results are very much similar to the results of the study conducted by Kumar *et al.*,[16] who also found negative correlation of age and CP scores with vitamin D levels. They did not, however, find any association of vitamin D levels with the etiology of liver diseases. In our study, we also did not find the etiology of liver cirrhosis to be as a predictor of low vitamin D levels.

Vitamin D deficiency is not only responsible for musculoskeletal manifestations but also many other complications in cirrhotic patients. Early decompensation and higher mortality rates are also attributed to vitamin D deficiency in these patients.[21] Many studies have also suggested that adequate replacement of vitamin D by using vitamin D supplements can improve the functional status, prognosis, CP score, model of end-stage liver disease score and overall morbidity of patients with liver disease. Therefore, it is recommended that this deficiency should be addressed promptly so that patients with chronic liver problems are benefited.[22]

Conclusions

Vitamin D deficiency is documented in the majority of patients afflicted by CLD, particularly those having advanced disease. As the disease advances, the levels become more deficient. Vitamin D levels should be routinely checked in all patients suffering from advanced CLD, so that adequate replacement by vitamin D supplements can be initiated as a therapeutic adjunct in managing such patients.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conception of study objectives and/or design, drafting of the article and revising the article for important intellectual

Table 4. Univariate and multinomial regression analyses showing the different variables to predict vitamin D deficiency in the study group

	Univariate analysis		Multinomial analysis		
Variable	OR (95% CI)	*p**	Chi-square value	OR (95% CI)	*p**
Age	3.72 (3.26–4.18)	**0.000**	70.48	1.26 (1.15–1.38)	**0.000**
Sex, female vs. male	1.69 (1.59–1.79)	**0.000**	46.65	–	**0.000**
Etiology of liver disease	1.50 (0.57–2.43)	0.523	0.738	–	0.947
MELD score	2.69 (2.35–3.03)	**0.000**	27.40	1.32 (1.14–1.52)	**0.000**
CP score	2.89 (2.51–3.26)	**0.000**	32.55	2.10 (1.46–3.01)	**0.000**
CP class	1.28 (1.10–1.47)	**0.000**	43.17	0.02 (0.002–0.18)	**0.001**

*Bold font indicates statistically significant values.

Abbreviations: CI, confidence interval; CP, Child-Pugh; MELD, model of end-stage liver disease; OR, odds ratio.

content (ZJ, AAD, NY), collection of data (SA, AK), analysis of data (ZJ, SA), interpretation of findings (ZJ, AK).

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