ORIGINAL ARTICLE

Serum Vitamin D Level as a Predictor of Severity of Chronic Liver Disease in Children in a Resource limited Country

NADIRA MUSABBIR, FAHMIDA BEGUM, MD WAHIDUZZAMAN MAZUMDER, SHARMIN MAHBUBA

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Correspondence to:

Dr. Nadira Musabbir,
Assistant Professor
Department of Pediatric Gastroenterology and Nutrition Bangladesh Medical University (former Bangabandhu Sheikh Mujib Medical University
Dhaka, Bangladesh.

E-mail: nadira_mou@yahoo.com

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ABSTRACT

Objective: To determine the role of serum vitamin D level in predicting the severity of CLD in children in a resource limited country.

Study Design: Cross-sectional study.

Place and duration of study: The study was conducted at Bangladesh Medical University, Dhaka, Bangladesh, from January 1, 2023 to December 31, 2024.

Material and Method: This cross-sectional study was done among 75 children with CLD between January 2023 and December 2024 at Bangladesh Medical University, Dhaka, Bangladesh. Child-Pugh class was used for assessment of severity of CLD and patients were categorized into three groups as Child-Pugh class A, B, and C. Vitamin D level was checked in all patients and labeled as: deficient (<20 ng/mL), insufficient (20–30 ng/mL), and sufficient (> 30 ng/mL).

Results: This study found that 81.3% of children with CLD had either vitamin D deficiency or insufficiency. Mean vitamin D level was 21.51 ± 8.64 ng/ml. Lower vitamin D levels were inversely correlated with Child-Pugh class of CLD (r = - 0.701, p = 0.000). On univariate analysis, serum vitamin D level, bilirubin, albumin, INR and Hb were found as predictor of severity of CLD, whereas in multivariate analysis, only serum vitamin D level was found as a predictor of severity (p = 0.029).

Conclusion: Most children with CLD had either vitamin D deficiency or insufficiency. Lower serum vitamin D level was found as a predictor of severity of CLD in children.

Keywords: *Vitamin D, Child- Pugh class, CLD, Children, Bangladesh*

INTRODUCTION

Chronic liver disease (CLD) is an irreversible disorder characterized by ongoing hepatocellular injury accompanied by compensatory repair process ultimately resulting in fibrosis and cirrhosis.[1] Globally around 1.5 billion per 100,000 people are burdened with chronic liver disease.[2] The common causes of CLD in children include chronic hepatitis B infection, biliary atresia, metabolic diseases, and autoimmune diseases.[3] If not appropriately managed, pediatric CLD can lead to a range of serious complications such as portal hypertension, hepatic encephalopathy, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatopulmonary syndrome.

Several scoring systems are used for assessment of severity of CLD in children. Among them, Child-Pugh (CP) score is the well-known parameter in children, which is based on five variables, with scores ranging from 5-15, allowing categorization into three severity classes: class A (5-6 points), class B (7-9 points) and class C (10-15 points).[4]

Vitamin D, which is a steroid hormone has different roles such as calcium homeostasis, cell proliferation and differentiation, immune modulation, and anti-inflammation, thus helps in protection from many diseases including liver diseases.[5] Liver diseases are known to interfere with vitamin D hydroxylation causing reduced active vitamin D metabolites. Also, patients with liver diseases have inadequate sun exposure, insufficient food intake, and vitamin D malabsorption because of decreased bile salt delivery to the small bowel. All these factors contribute to vitamin D deficiency, which induces metabolic liver disease termed hepatic osteodystrophy.[6,7,8,9,10]

Recent published literature reported that the global occurrence of Vitamin D deficiency (VDD) across all age groups range from 20%- 100%.[11] In children, the prevalence of VDD is around 85 to 98%.[12] Up to 10% to 36% of children with cholestatic liver disease have been reported to have VDD.[13] Study done in adult population revealed that 64% to 92% of patients with CLD have VDD[10] and they are more prone to develop bacterial infection, portal hypertension, and severe hepatic fibrosis along with an increased rate of mortality.[9]

The serum vitamin D status in children with chronic liver disease, as well as its association with disease severity is not well established in pediatric age group. This area of research needs to be explored more so that if serum vitamin D level is found as a predictor of severity of CLD in children, then adequate supplementation of vitamin D will help to halt the progression of liver fibrosis, thus decrease both the morbidity and fatality related to liver diseases in children.

In this study, we aimed to determine whether serum vitamin D level can be used as a predictor of severity of CLD in children.

MATERIAL AND METHODS

This cross-sectional study took place in Pediatric Gastroenterology and Nutrition Department at Bangladesh Medical University (former Bangabandhu Sheikh Mujib Medical University), Dhaka, Bangladesh, over a two-year period from January 1, 2023 to December 31, 2024. This study got ethical clearance from institutional review board.

A sample size of 75 was determined, taking into account the number of CLD patients admitted into hospital, and length of the study. Patients younger than 18 years with a diagnosis of chronic liver disease were enrolled in this study. Individuals were excluded if they had a prior history of vitamin D or calcium supplementation, or were receiving medications known to influence vitamin D metabolism (such as anticonvulsants, corticosteroids, or rifampicin). Additionally, patients with coexisting conditions, that could interfere with vitamin D metabolism, including chronic kidney disease or malabsorption syndromes, were not included.

A comprehensive history was obtained, and a complete physical examination of each patient was done by the principal investigator and all findings documented using a standardized data collection form.

Blood samples from each patient were collected for complete blood count, serum albumin, serum bilirubin, prothrombin time, international normalization ratio (INR), and serum vitamin D level. Vitamin D level (25-hydroxyvitamin D) was

measured using the immunoassay method. The cut-off value set for serum vitamin D levels were as follows: level below 20 ng/ mL were considered deficient, 20-30 ng/mL as insufficient, and > 30 ng/mL as sufficient.[12] Serum bilirubin and albumin were measured by photometry method in the Department of Biochemistry and Molecular Biology. Prothrombin time (PT) estimation was done in the Department of Hematology by using the Sysmex CA650 Coagulation analyzer and international normalized ratio (INR) was derived from patient's PT in comparison with the control value.

Transabdominal ultrasonography was done on all patients by an expert radiologist for grading of ascites (if present), as either mild or marked. Hepatic encephalopathy was also assessed by the physician during physical examination.

Child-Pugh classification was used to classify the patients into three classes. This classification is based on five variables: the presence of ascites, degree of encephalopathy, and serum levels of bilirubin (mg/dl), albumin (g/dl), and prothrombin time (seconds). Each variable is assigned a scored from 1 to 3, and the total score is calculated to label the patients as class A (5-6 points), class B (7-9 points), and class C (10-15 points).[4]

Numerical variables were presented as mean, and standard deviation or median, as appropriate, whereas categorical variables were summarized as frequency and percentage. Chi-square test and spearman's rank correlation coefficient test were applied to evaluate the association between vitamin D categories and the Child-Pugh classes of CLD. Univariable and multivariable logistic regression analysis was done to identify predictors of disease severity. A p-value <0.05 was considered statistically significant. Statistical analysis was done by using IBM Statistical Packages for Social Sciences (SPSS) version 25 software

RESULTS

The study population had a mean age of 7.5 ± 4.45 years, ranging from 4 months to 16 years. A male predominance (60%) was noted with male to female ratio of 3:2.

Among the 75 studied patients, 33 (44%) were diagnosed as Wilson disease, whereas biliary atresia, and autoimmune hepatitis, each constituted for 14 (18.66%) cases. Budd-Chiari syndrome (2; 2.66%), Caroli syndrome (1; 1.33%), primary sclerosing cholangitis (1;1.33%), and Alagille syndrome (1;1.33%) were among the other identified causes. In 9 (12%) cases, specified cause remained undetermined.

Out of 75 patients, 18 belonged to Class A, 27 to Class B, and 30 to Class C. Table 1 showing the baseline laboratory profiles

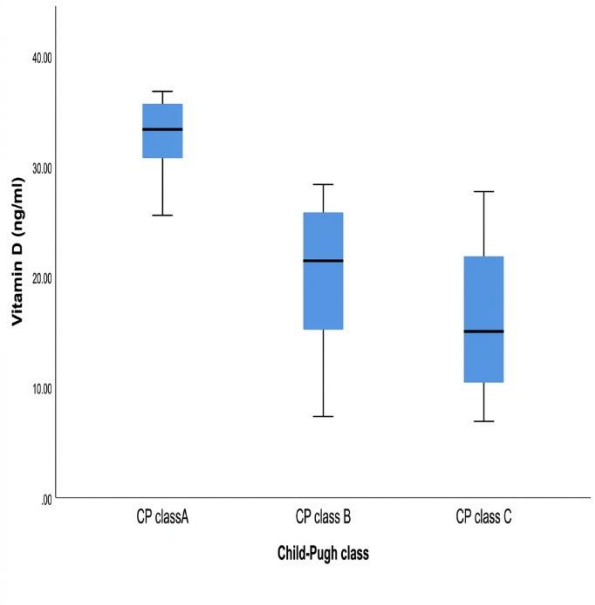
Table 1: The baseline laboratory profile of the study population (n = 75)

Variables	Value (n=75)
Hemoglobin (g/dl; mean ± SD)	9.82 ± 1.58
WCC (x 10^3 /mm^3; mean ± SD)	10.22 ± 8.49
Platelet (x 10^3/ mm^3; mean ± SD)	198.82 ± 117.02
Bilirubin (mg/dl; median, range)	2.8 (0.30-27.98)
ALT (U/L; median, range)	96 (8-922)
INR (mean ± SD)	2.14 ± 1.55
Albumin (g/dL; mean ± SD)	2.89 ± 0.69
CP score (mean ± SD)	8.63 ± 2.57
Vitamin D level (ng/ml; mean ± SD)	21.51 ± 8.64

Abbreviations: WCC, white cell count; ALT, alanine aminotransferase; INR, international normalized ratio; CP, Child-Pugh

Among the studied patients, 34(45.3%) patients had vitamin D deficiency, 27(36%) patients had insufficient vitamin D, and 14(18.7%) patients had sufficient levels. The mean vitamin D concentrations across different classes of CLD are illustrated in Figure 1

Fig 1: Mean serum vitamin D level in different CP classes of CLD among study population (n = 75)



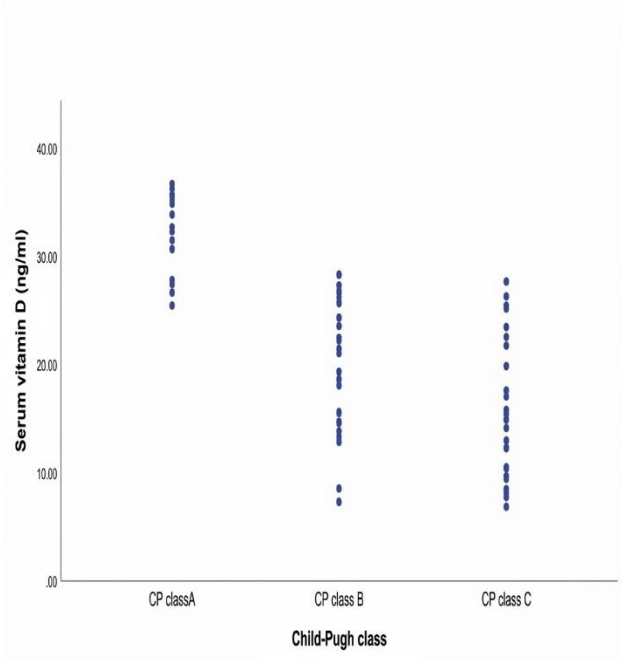
None of the patients of CP class B or class C had sufficient vitamin D levels, but 14 (77.8%) of class A had vitamin D sufficiency. However, 22 (73.3%) of CP class C and 12 (44.4%) of class B had vitamin D deficiency whereas none of class A had deficient vitamin D levels. Additionally, 8(26.7%) of class C, 15 (55.6%) of class B and 4 (22.2%) of class A had vitamin D insufficiency. There was a significant association between reduced vitamin D levels and the severity of chronic liver disease in children (Table 2).

Table 2: Association of vitamin D categories with Child Pugh class of CLD (n=75)

	Child Pugh Class			
Serum vitamin D	A (n = 18)	B (n =27)	C (n=30)	P value
Deficient	0	12 (44.4%)	22 (73.3%)	0.000
Insufficient	04 (22.2%)	15 (55.6%)	08 (26.7%)	
Sufficient	14 (77.8%)	0	0	

A significant negative correlation was identified between vitamin D levels and the Child-Pugh Class in child with CLD (correlation coefficient = - 0.701, p = 0.000) using Spearman correlation coefficient test (Figure 2).

Fig 2: Scatter diagram showing the correlation of serum vitamin D levels and Child Pugh class of CLD (n=75)



On univariate regression analysis using C-P score >6 as cutoff point between compensated and decompensated CLD, serum vitamin D level (p = 0.008), bilirubin (p = 0.013), albumin (p = 0.000), INR (p = 0.002), and Hb (p = 0.012) were found as predictor of decompensation and taken up for multivariate analysis. On multivariate regression analysis, only serum vitamin D level was found to have significant (p = 0.029) association with severity of CLD (Table 3)

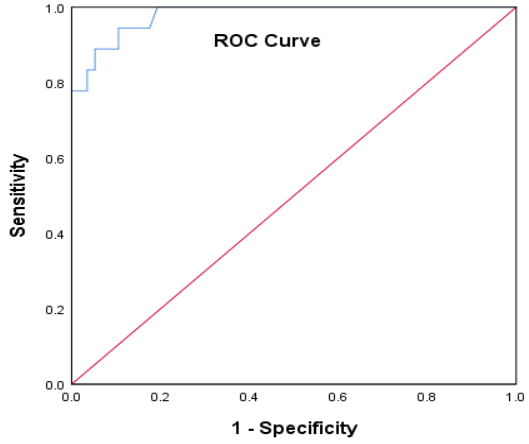
Table 3: Logistic regression predictors of CLD severity

Variables	Univariate Logistic Regression		Multivariate Logistic Regression	
	OR (95% CI)	P value	OR (95% CI)	P value

Serum vit D, ng/ml	0.424 (0.225-0.800)	0.008	1.984 (1.074-3.663)	0.029
Bilirubin, mg/dl	1.839 (1.137-2.975)	0.013	0.877 (0.577-1.332)	0.538
Albumin, g/dl	0.013 (0.001-0.127)	0.000	32.228 (0.279-3727.19)	0.152
INR	6.984 (2.020-24.146)	0.002	1.067 (0.309-3.684)	0.919
Hb, g/dl	0.565 (0.362-0.882)	0.012	1.131 (0.507-2.524)	0.763
Age, yrs	0.921 (0.813-1.043)	0.193		

In our study, the area under the ROC, with 95% CI, for serum vitamin D level in predicting CLD severity was found 0.97 (95% CI: 0.952-1) (p = 0.000) (Figure 3).

Fig 3: Receiver operating characteristic curve for serum vitamin D level in predicting severity of CLD



DISCUSSION

Vitamin D deficiency has become an emerging public health problem affecting 30-50% of children globally.[14] The prevalence of VDD is also high in tropical countries like India, and Malaysia, where there is adequate sun exposure throughout the year.[14,15]

Numerous studies have reported that hypovitaminosis D is highly prevalent among patients with CLD and reduced vitamin D level is linked to more advanced stages of cirrhosis [6,8, 16, 17] and increased risks of fatality.[9] So, vitamin D levels can be used to predict the severity of cirrhosis in children.

Various pediatric studies are done among CLD patients to know their vitamin D status. Hourigan et al. found that 78% of 102 children with non-alcoholic liver disease had sub optimal vitamin D levels.[5] In another Malaysian study of children with CLD receiving vitamin D supplementation, 28% were found to have vitamin D deficiency or insufficiency.[10] Furthermore, another study on 23 children with cholestatic liver disease revealed that 82% of their study population had vitamin D deficiency.[18]

Due to variability in the cut off values used to define vitamin D categories across different studies, it was challenging to compare our study findings with that of others. In our study, more than two-thirds of the study subjects had either vitamin D deficiency or insufficiency with a mean vitamin D level of 21.99 ± 8.73 ng/ml.

Several adult studies have reported reduced vitamin D levels among patients with CLD, consistent with our study findings. In a study involving 100 CLD patients, 91% were found to have subnormal vitamin D levels.[19] Similarly, Jamil et al found that 88% of cirrhotic patients in Pakistan had either vitamin D deficiency or insufficiency, and their mean vitamin D levels were significantly lower than those of the control group. [8]

Several factors predispose to vitamin D deficiency in CLD patients, including impaired hepatic hydroxylation of vitamin D to 25(OH) D, inadequate sun exposure, inadequate dietary intake, and reduced vitamin D absorption.[11]

However, In Bangladesh, 75% of healthy children are also suffering from hypovitaminosis D due to less sunlight exposure, skin pigmentation, and air pollution.[20] As in our study, we have not included any healthy children as control group so no comparison of vitamin D level was done between healthy children and CLD patients.

In this current study, a significant association was observed between vitamin D status (deficient, insufficient and sufficient) and Child- Pugh classification of CLD. A significant negative correlation was also identified between serum vitamin D levels and Child-Pugh class. Children with lower vitamin D level had higher Child-Pugh scores, indicating more advanced disease severity. Our study finding is supported by other studies done by Patel et al, Verma et al, Jamil et al, and Hussein et al.[8,19, 21] However, a study by Capul et al on cholestatic children reported no significant association between vitamin D level and disease severity, which contrasts with our result.[13]

On univariate logistic regression analysis, serum vitamin D level, bilirubin, albumin, INR, and Hb were found as predictors of severity of CLD. However, on multivariate logistic regression analysis, only serum vitamin D level was found as an independent predictor.

Our study had several limitations. As a cross-sectional design, follow up of patients after vitamin D supplementation were not performed. There was no control group in our study and also sample size was relatively small, so further studies with control group and larger sample size are needed to better elucidate the association between low vitamin D levels and the severity of CLD in children.

CONCLUSION

Majority of children with chronic liver disease had either a deficient or insufficient level of vitamin D. Lower serum vitamin D levels were found to be a significant predictor of disease severity in CLD. So, vitamin D level should be routinely assessed in all CLD patients to help evaluate disease severity. Adequate supplementation of vitamin D as a therapeutic adjunct may also help to stop the progression of disease severity.

Abbreviations:

CLD: Chronic liver disease

PT: Prothrombin time

INR: International normalization ratio

CP: Child-Pugh

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Conflict of interest:

There is no conflict of interest (ICMJE form attached)

Authors' affiliation

Dr. Nadira Musabbir,
Assistant Professor
Department Pediatric Gastroenterology
Bangladesh Medical University
Dhaka, Bangladesh.

Dr. Fahmida Begum,
Associate Professor
Department Pediatric Gastroenterology
Bangladesh Medical University
Dhaka, Bangladesh

Dr Md Wahiduzzaman Mazumder,
Associate Professor
Department Pediatric Gastroenterology
Bangladesh Medical University
Dhaka, Bangladesh

Dr. Sharmin Mahbuba,
Assistant Professor
Pediatric Endocrinology
Department of Pediatrics
Bangladesh Medical University
Dhaka, Bangladesh

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Author's Contribution

NM : Proposed topic, basic study design, methodology and manuscript writing
FB: Data collection, statistical analysis and interpretation of results,
MWM: Literature review & referencing and quality insurer
SM: concept of study and acquisition of date.

All the authors have approved the final manuscript draft and accept the responsibility of research integrity.