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Vitamin D Status And Its Association With Child-Pugh Class In Chronic Liver Disease: A Cross-Sectional Observation In A Tertiary Center Of Northern Bangladesh

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Abstract
Background: *The association of vitamin D status with chronic liver disease (CLD) has gained considerable attention, considering its potential role in disease progression and complications. The present study aimed to assess vitamin D in patients with CLD and to evaluate its relationship with disease severity through Child-Pugh class in a tertiary health care center of Rajshahi, a division of north Bangladesh.*
Method: *Being cross-sectional by design, this study enrolled 181 adult CLD patients admitted in the Department of Medicine and Hepatology, Rajshahi Medical College Hospital. Following ethical approval and ensuring informed consent from each patient, data were collected through face-to-face interviews, clinical examinations, and laboratory tests (serum bilirubin, albumin, INR, hepatitis serology, and vitamin D levels). Child-Pugh scores were assigned based on specific criteria. Vitamin D deficiency was defined based on predetermined thresholds. Separate case record form was used for data collection. Statistical analysis was conducted using SPSS V 25.*
Result: *The mean age of the study patients was 51.01 ± 13.41 (SD) years with 68% male. In terms of disease severity based on the Child-Pugh class, 11% of the participants were classified as class A, 49.2% as class B, and 39.8% as class C. About 81.2% of the patients had vitamin D deficiency while 10.5% had insufficient vitamin D level and only 8.3% had sufficient vitamin D level. The median of vitamin D was 12.7 ng/ml (2.3ng/ml-52.8ng/ml). The status of vitamin D level was significantly associated with Child-Pugh class where more severe form of disease (class C and class B) had higher number of patients with vitamin D deficiency (p<.05). The median value of vitamin D was also significantly lower in patients of class C (9.5 ng/ml) than class B (12.8ng/ml) and class A (21.45 ng/ml) (p<.05). A strong negative correlation (rho=-.471) was also observed between Child-Pugh score and vitamin D with statistical significance (p<.05).*
Conclusion: *This study observed a concerning incidence of vitamin D deficiency in CLD patients along with a significant negative relation with Child-Pugh score and disease severity. Further research with larger and more diverse populations is needed before implementing a strategy using this finding.*
Keywords: *Vitamin D, Chronic Liver Disease, CLD, Child-Pugh class, Child-Pugh score, Bangladesh, 1,25-dihydroxyvitamin D*

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I. Introduction

Vitamin D is a seco-steroid hormone playing key roles in skeletal functions, immune regulations and cellular functions [1]. Optimal vitamin D status is associated not only in maintaining these physiological functions but also associated with many chronic conditions including chronic liver disease (CLD) [2]. CLD is a significant cause of global mortality and morbidity with a diverse etiologies and progressive nature [3].

Vitamin D deficiency has become epidemic worldwide in past decade [4] and its association with CLD has also well been established [5]. Few studies also showed that vitamin D status of CLD patients as a potential indicator of disease progression and outcomes in CLD [6, 7]. The severity of CLD is often assessed using the Child-Pugh scoring system, which incorporates clinical and laboratory parameters to stratify patients into different classes (A, B, or C). The scoring and stratification is conducted based on the extension of hepatic function parameters- serum bilirubin, albumin, international normalized ratio (INR) and the presence and severity of clinical complications- ascites and hepatic encephalopathy. As CLD is a progressive disorder involving complex mechanism, these patients should be frequently screened for further progression of disease to ensure a management targeting prevention or at least highest possible delayed worsening. In resource limiting settings like Bangladesh, frequent assessment through Child-Pugh score is inconvenient due to unavailability of laboratory facilities and also for high cost.

So, if an association between vitamin D status and Child-Pugh class could be established for the population of Bangladesh, assessment of vitamin D could be an alternate routine prognostic parameter to screen out the vulnerable patient group for further assessment. Hence, the severity of CLD as determined by the Child-Pugh class remains an area of ongoing investigation.

In this context, the present study aimed to evaluate the relationship between vitamin D and the severity of CLD within the framework of the Child-Pugh scoring system. By understanding this relationship, we hope to improve how we identify and treat different stages of liver disease. This could lead to better strategies for assessing risks, providing treatments, and designing care plans that meet the unique needs of people with CLD.

II. Methods

Utilizing a cross-sectional approach, this study enrolled adult (≥ 18 years) patients admitted with a confirmed diagnosis of chronic liver diseases (CLD) at Department of Hepatology and Medicine, Rajshahi Medical College Hospital (RMCH). RMCH is one of the prime tertiary health centers in Northern Bangladesh and offer government facilitated tertiary health care to the population residing nearby area. This hospital was selected as study place to capture a diverse group of patients residing this area which remains often unexplored.

Ethical approval was obtained before commencing the study. This study included 181 CLD patients through purposive sampling. Patients with a history of diagnosis of chronic kidney disease, malabsorption syndrome, tuberculosis, hepatocellular carcinoma, other malignancies were excluded. History of certain medications which affect serum vitamin D level were also excluded (calcium and vitamin D supplements, steroids, antiepileptic drugs and bisphosphonates). Written informed consent was ensured prior inclusion in this study.

Data were collected via detailed face to face interviews and clinical examinations. Laboratory tests were conducted for assessment of serum bilirubin, albumin, INR, hepatitis serology, and 25-hydroxyvitamin D levels. An ultrasound was performed for ascites evaluation, and hepatic encephalopathy was clinically graded for each patient by an expert physician.

Child-Pugh scores were assigned based on ascites, hepatic encephalopathy, serum bilirubin, INR, and albumin levels. Patients without ascites or encephalopathy, with serum bilirubin <2 mg/dL, albumin >3.5 g/dL, and INR <1.7 were assigned as Child-Pugh class A [8]. Those with mild to moderate ascites or grade 1-2 encephalopathy, bilirubin 2–3 mg/dL, albumin 2.8–3.5 g/dL, and INR 1.7–2.3 were categorized as class B. Severe CLD cases with significant ascites or grade 3-4 encephalopathy, bilirubin >3 mg/dL, albumin <2.8 g/dL, and INR >2.3 were classified as class C.

Vit-D deficiency was defined as vitamin D levels <20 ng/mL, vitamin-D level between 21 ng/mL to 30 ng/mL was considered insufficient vitamin D and above 31 ng/mL was considered as sufficient [9]. For assessment of vitamin D radioimmunoassay (ELFA assay) was considered.

A pre-tested semi-structured questionnaire facilitated data gathering to ensure consistency and reliability in our findings.

Statistical analysis: Data was meticulously entered, verified, and analyzed using Microsoft excel and SPSS version 25. Normality or distribution of the quantitative variables were explored through Shapiro-Wilk test where rejection of null hypothesis ($p \leq .05$) indicates non-parametric distribution of data. Quantitative data were summarized as means, standard deviations for parametric data and as median, minimum, and maximum value for non-parametric data. Qualitative data were represented as frequencies and percentages. Statistical comparisons utilized the Chi-Square test for categorical data and independent samples Kruskal-Wallis test for continuous

variables when applicable, considering p-values < 0.05 as significant. Results were displayed through text, tables, and graphical figures.

Ethical issues: Ethical integrity was paramount in this study following 'Declaration of Helsinki'. Ethical clearance obtained from ethical review committee of RMCH. Strict confidentiality of participant data was upheld. Informed consent was obtained following a clear and brief explanation of the study's nature, procedures, and the participant's rights to decline or withdraw without consequence. Participants received no financial incentives for participating in this study.

III. Result

The baseline characteristics of the study patients with chronic liver disease are tabulated in Table 1. The majority of the study patients belonged to the age group 51-60 years with a mean of 51.01±13.41 (SD) years. Males represented two-third of the study population. The most common etiology of CLD was Hepatitis B virus, followed by non-alcoholic fatty liver disease (NAFLD) and Hepatitis C virus. **(Table 1)**

In terms of disease severity, nearly half of the participants (49.2%) were classified as Child-Pugh class B, with a significant proportion (39.8%) in class C. Only 11% were classified as Child-Pugh class A, representing the least severe form of liver disease. **(Table 1)**

Table 1: Baseline characteristics of the study participants (n=181)

Variables	n	%
Age group (years)		
18-30	13	7.2
31-40	38	21
41-50	33	18.2
51-60	62	34.3
61-70	23	12.7
>70	12	6.6
Mean±SD	51.01±13.41	
Gender		
Male	123	68
Female	58	32
Etiology		
Hepatitis B virus	82	45.3
Non-alcoholic fatty liver disease	37	20.4
Hepatitis C virus	35	19.3
Cryptogenic	20	11
Wilson	7	3.9
Severity according to Child-pugh class		
Class A	20	11
Class B	89	49.2
Class C	72	39.8

Approximately four-fifth of the study patients with CLD had a deficient level of vitamin D, 10.5% had insufficient vitamin D. Only 10.5% had sufficient level of vitamin D. **(Figure 1)**

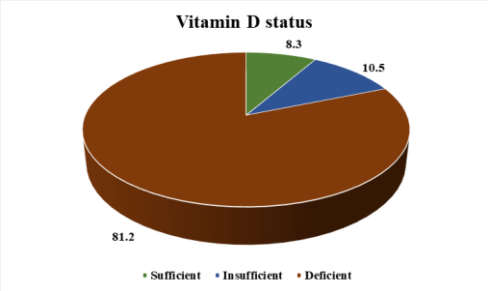

Figure 1: Vitamin D status among the study patients with CLD (n=181)

Highest proportion of patients with vitamin D deficiency is found in Class C, followed by Class B, and then Class A. On the other hand, patients with sufficient vitamin D levels are mostly found in Class A, while only a few are in Class B. So, vitamin D status in significantly associated with the severity of CLD where vitamin D tends to decrease with the increase of severity of the condition (p=<.001, determined by chi-square test). **(Figure 2)**

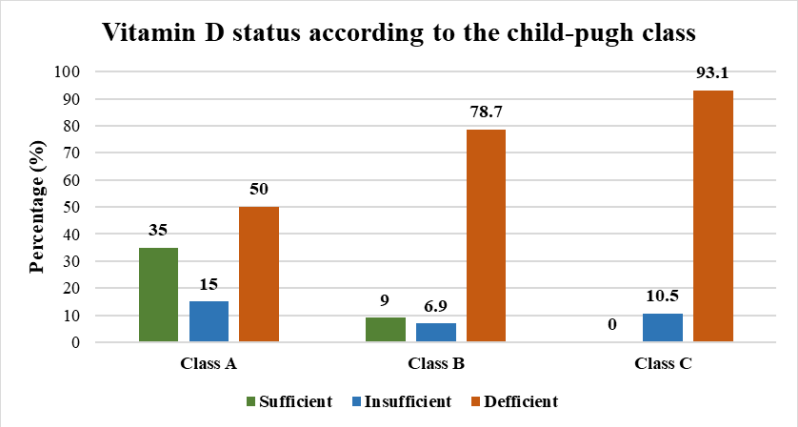

Figure 2: Vitamin D status of the study patients with CLD according to Child-Pugh class (n=181)

Median value of vitamin D in study patients was 12.7 ng/ml (2.3 ng/ml – 52.8 ng/ml). Median value of vitamin D level was significantly low in class C patients than class B and A. **(Table 2)**

Table 2: Difference of serum vitamin D level across the study patients of child-pugh class A, B and C (n=181)

		Child-pugh class			p value*
	Total n=181 Median (Min-Max) ng/ml	Class A n=20 Median (Min-Max) ng/ml	Class B n=89 Median (Min-Max) ng/ml	Class C n=72 Median (Min-Max) ng/ml	
Serum vitamin D	12.7 (2.3–52.8).	21.45 (13.10-36.07)	12.80 (2.30-52.80)	9.50 (3.50-22.40)	**<.001**

***p value was determined by independent samples Kruskal-Wallis test**

A significant negative linear correlation was observed between Child-Pugh score and vitamin D level where vitamin D decreases with the increase of Chipd-Pugh score (rho=-.471, p<.001, p value was determined by spearman rank test). **(Figure 3)**

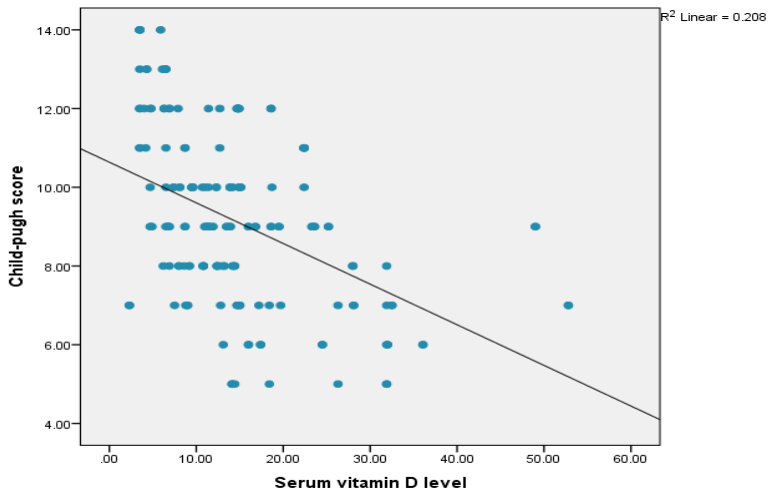

Figure 3: Scatter plot diagram showing correlation between child-pugh score and serum vitamin D level (n=181)

IV. Discussion

In the present study, the proportion CLD patients with vitamin D deficiency was very high with a percentage of 81.2. Moreover, a strong relationship between vitamin D level and the severity of CLD has been demonstrated where vitamin D significantly decreases with the worsening of liver function. These findings are consistent with previous research conducted across the globe [10–12].

The severity of CLD was assessed in this study by Child-Pugh score, a widely used clinical tool combining both clinical and laboratory parameters [13]. According to Child-Pugh scores- the CLD patients are divided into three classes A, B and C where class C indicates the most severe form of the condition or worst hepatic function, class B indicates the moderate level and class A indicates the least severity. The association between vitamin D status and the Child-Pugh class was statistically significant in this study where Class C and Class B had more patients with deficient vitamin D levels than Class A. This association is further emphasized by the observed differences in vitamin D levels across the different classes where the median serum vitamin D level was significantly lower in class C patients compared to class B and class A patients. This indicates that as the severity of liver disease increases, there is a concurrent decrease in vitamin D levels. These findings support the notion that vitamin D deficiency may be associated with more advanced stages of CLD. Moreover, a strong negative linear correlation was demonstrated in this study between Child-Pugh score and Vitamin D. These findings corroborate with several previous studies [14–17]. Several mechanisms are considered to responsible behind these relation between decreasing of vitamin D and worsening of liver function. Liver dysfunction associated with CLD might lead to impaired synthesis and activation of vitamin D, contributing to decreased circulating levels of this essential nutrient [18]. Furthermore, chronic inflammation and altered metabolism associated with advanced stages of liver disease may further exacerbate the decrease in vitamin D levels [19]. Individuals with compromised hepatic function often experience limited sun exposure, which is a primary source of vitamin D synthesis in the body. These factors might collectively contribute to the observed decrease in vitamin D levels in patients with worsening hepatic function.

This study found that hepatitis B virus was the most common cause of CLD, followed by non-alcoholic fatty liver disease (NAFLD) and hepatitis C virus. These findings also corroborate with other studies [20, 21]. These etiological factors also may have played on the vitamin D status of the study patients, as chronic inflammation and hepatic dysfunction associated with viral hepatitis and NAFLD can lead to altered vitamin D metabolism and decreased levels [22].

Regarding age and gender distribution of the study patients the observed average age (51 years) and male predominance (two-third of total study patients) are supported by previous similar studies [23–26].

The high prevalence of vitamin D deficiency among patients with CLD in a tertiary center of Northern Bangladesh emphasizes the need of screening for vitamin D status among the patients with compromised hepatic function. Moreover, the follow up of CLD includes various investigations and clinical assessments all of which are not widely available in Bangladesh and also not cost-friendly. On other hand, single assessment of vitamin D could be considered as part of routine management while other investigations and seeking specialist consultation is not convenient. Additionally, strategies to address vitamin D deficiency, such as supplementation or lifestyle modifications, may be beneficial in improving outcomes and potentially slowing down disease progression in CLD patients.

This study is not beyond limitations. The cross-sectional design limits the opportunity of multiple follow-ups over the disease course. Alongside it was not possible to establish a causal relationship vitamin D of CLD patients with healthy control. Additionally, the study was conducted in a specific geographic region and may not be representative of other populations. Further research involving larger sample sizes and diverse populations is essential to validate these findings.

V. Conclusion

This study provides evidence of vitamin D status among the patients with chronic liver disease (CLD) residing in Northern Bangladesh. The high proportion of vitamin D deficiency among CLD patients highlights the need for routine screening and management strategies to address this deficiency. Future research should be conducted before considering interventions to optimize vitamin D status in this patient population.

Declarations:

Ethics approval: The study protocol was reviewed and approved by the Ethical Review Committee of Rajshahi Medical College. Ethical issues were maintained in accordance with the Helsinki Declaration.

Consent for publication: none

Availability of data and materials: The data and other necessary details are available and can be found upon reasonable request to the corresponding authors.

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