

## Original Research Article

# A study of the correlation of serum vitamin D levels to Child-Pugh and MELD-Na scoring system in cirrhosis of the liver

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### ABSTRACT

**Background:** Vitamin D is a hormone with known effect on calcium homeostasis, but recently there is increasing recognition that it also is involved in cell proliferation and differentiation, has immunomodulatory and anti-inflammatory properties. These effect may explain its importance in the liver diseases. Vitamin D deficiency has been reported highly prevalent in Chronic liver disease (CLD) and there is an emerging interest to explore the relationship of vitamin D deficiency and severity of CLD. The aim of the study was to evaluate the correlation of serum vitamin D levels to the Child Pugh and MELD-Na scoring system in liver cirrhosis and to establish its relationship with the severity of the disease.

**Methods:** Serum vitamin D levels were measured in 100 patients of CLD and 100 healthy controls. The degree of liver dysfunction was estimated by Child-Pugh and MELD-Na scores.

**Results:** 91% of the CLD patients had subnormal vitamin-D levels. The mean vitamin D level in CLD patients was lower ( $15.97 \pm 7.45$ ) than controls ( $30.12 \pm 6.60$ ) with statistical significance ( $p = 0.0001$ ). On linear regression vitamin D level showed significant negative correlation with Child Pugh score ( $r = -0.446$ ,  $p < 0.001$ ) and MELD score ( $r = -0.395$ ,  $p < 0.001$ ). Low vitamin D level was associated with poor outcome (mean vitamin D level  $9.61 \pm 3.01$  who died versus  $16.52 \pm 7.47$  who survived and discharged).

**Conclusions:** CLD is associated with a significantly low level of vitamin D. The lower level of vitamin D is associated with severity of CLD, mortality and increased risk for complications. Awareness of serum vitamin D level in CLD patients is important to improve outcome.

**Keywords:** MELD score, CLD, Vitamin D, Child-Pugh score

### INTRODUCTION

Vitamin D is a secosteroid hormone, which is mostly known as regulator of calcium and bone metabolism. Vitamin D deficiency is extremely common in chronic liver disease patients. Upto 93% of these patients have some degree of Vitamin D deficiency.<sup>1,2</sup> Even patients with mild liver disease are affected, although liver cirrhosis patients most commonly suffer from severe deficiency.

Several studies in patients with liver cirrhosis have shown that Vitamin D deficiency has been associated with increased mortality bacterial infections portal hypertension complications<sup>6</sup> and fibrosis severity.<sup>3-8</sup>

Severe liver disease decreases vitamin D hydroxylation and albumin and DBP production, all of which are linked to low levels of Vitamin D.<sup>9</sup> Nevertheless, Vitamin D deficiency in chronic liver disease is only partly the result of synthesis dysfunction of liver.<sup>4</sup> Vitamin D deficiency in chronic liver disease requires several causes in addition to

the mentioned above, including inadequate sun exposure, insufficient food intake, steroid use, jaundice related deterioration of vitamin synthesis on the skin and decreased vitamin D absorption caused by intestinal edema secondary to portal hypertension or to cholestasis induced bile salt disruption.

Cirrhosis can be stage clinically. A reliable staging system is the Child-Pugh classification. Recently, the Child-Pugh system has been replaced by Model for End-Stage liver Disease (MELD-Na) system for listing a patient as a candidate for liver transplantation. The MELD-Na score is a prospectively derived system designed to predict the prognosis of patients with liver disease and portal hypertension. This score is calculated from four non-invasive variables: the prothrombin time expressed as the international normalized ratio (INR), the serum bilirubin level, the serum creatinine concentration and the serum sodium level.<sup>11,12</sup>

This study has been designed to evaluate the correlation of serum Vitamin D levels to the Child Pugh and MELD-Na scoring system in liver cirrhosis and to establish that serum vitamin D levels in cirrhotics indicates the severity of the disease.

## METHODS

This study was a single centre prospective case control study, performed after approval from the institutional ethical committee and written and well informed consent from total 100 patients of cirrhosis of liver admitted under Department of General Medicine at RNT Medical College and Associated Group of Hospitals, Udaipur (Raj), between January 2018 to December 2018.

100 healthy controls were selected from volunteers, general public, patients attendants and hospital staff.

### Inclusion criteria

The patients of either sex aged between 15 and 70 years were enrolled in the study after being diagnosed as cirrhosis liver (based on clinical, biochemical and radiological profile) due to any cause with or without hepatic encephalopathy.

### Exclusion criteria

Pregnancy or lactation, patients suffering from chronic disease like chronic renal failure, tuberculosis, malignancy, patient already taking Calcium and vitamin D supplementation, steroids and patients who were not giving consent for the study.

### Study design

Venous sample of eligible candidates were taken in an overnight fasting state in the mornings and were analysed by Electrochemiluminescence Immunoassay. For the

analysis the autoanalyzer used was HITACHI ROCHE COBAS e 601 autoanalyser available in concerned laboratory in our institution. Normal reference value of serum vitamin D level is 30-70 ng/ml.

### Methods of collection of data

Data was collected from a total of 100 patients of cirrhosis of liver. Detailed history and complete clinical examination of patients was carried out. A relevant drug history was also taken to exclude patients on drugs that are known to influence the vitamin D levels.

The blood samples of patients were taken and sent for complete blood count, renal function test, liver function test, 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. Upper gastrointestinal endoscopy and ultrasonography abdomen were done in all the patients.

Blood 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 Healthcare 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 Stago BT3203A337 coagulation analyzer.

Patients were scored according to Child-Pugh classification and classified into three classes: A, B and C. MELD score for all the patients were calculated as follow:

$$MELD = (0.957 \times \log_e \left( \text{creatinine} \frac{mg}{dl} \right) + 0.378 \times \log_e \left( \text{bilirubin} \frac{mg}{dl} \right) + 1.12 \times \log_e (INR) + 0.643) \times 10$$

For candidate with an initial MELD score greater than 11, the MELD score is then recalculated as follow; [44,45]

$$MELD - Na = MELD + 1.32 \times (137 - Na) - (0.033 \times MELD \times (137 - Na))$$

Serum vitamin D levels were also measured in the control group.

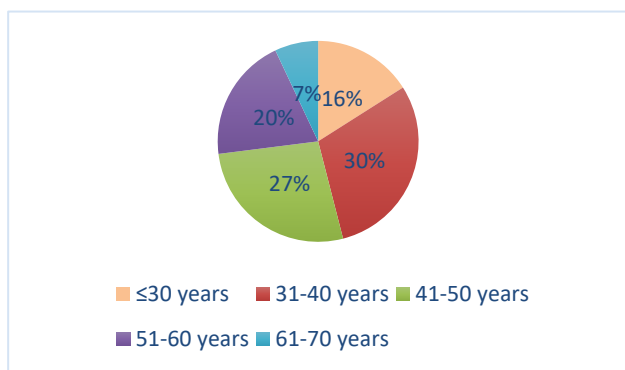
### Data analysis

At the end of the study, the data was compiled, tabulated and analysed. 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 Child-Pugh scores, MELD-Na scores

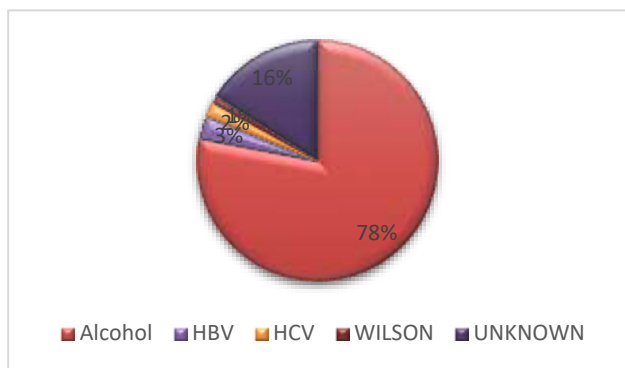
of liver cirrhosis and also with other variables. Correlation analyses were also carried out to find additional predictors of vitamin D deficiency in the disease group. Statistical package for social sciences (SPSS) version 16.0 software was used for analysing the data.

**RESULTS**

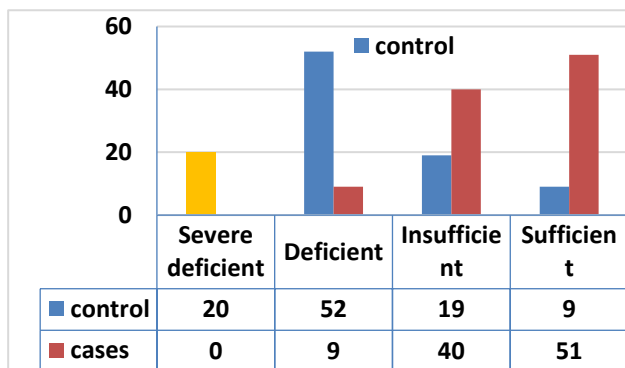
In the study population i.e. cases, 77 (77 %) were males and remaining 23(23%) were females. Most of patients (57%) were between the age of 31 to 50 years. The youngest cirrhotic was 22 years, the oldest being 65 years. The mean age of cases was 42.92±10.90 years.



**Figure 1: Distribution of cases in various age groups.**

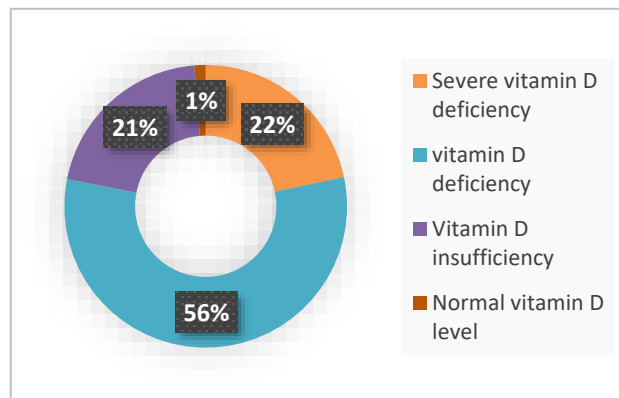


**Figure 2: Observed etiology in the cases.**



**Figure 3: Vitamin D status in cases and controls.**

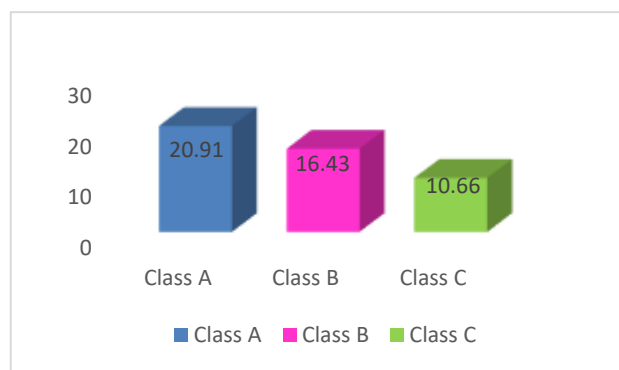
Alcohol was the most common cause of CLD in males and cryptogenic CLD was common in females. The etiology for liver disease in the study group ranged from alcohol, viral (Hepatitis B, C), Wilson disease to cryptogenic.



**Figure 4: Vitamin D status in the CLD patients.**

**Table 1: Relation of vitamin D levels with CP class of cirrhosis of the liver.**

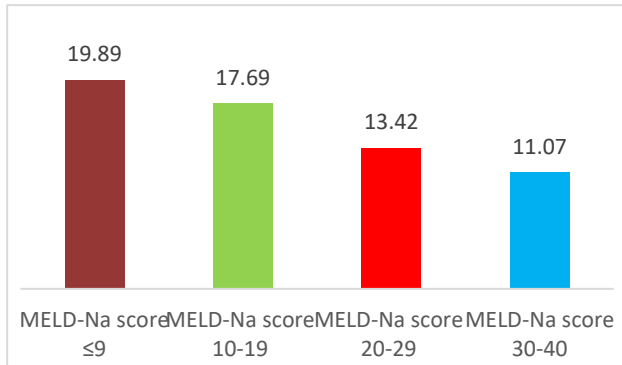
	Child Pugh (CP) class			Total
	A	B	C	
<b>Severe deficient</b>	0 (0%)	9 (16.9%)	11 (44.0%)	20 (20%)
<b>Deficient</b>	10 (45.5%)	29 (54.7%)	13 (52.0%)	52 (52%)
<b>Insufficient</b>	7 (31.8%)	11 (20.7%)	1 (4.0%)	19 (19%)
<b>Sufficient</b>	5 (22.7%)	4 (7.5%)	0 (0%)	9 (9%)
<b>Total</b>	22 (100%)	53 (100%)	25 (100%)	100 (100%)



**Figure 5: Mean value of vitamin D level in relation to Child-Pugh score.**

Patients and healthy controls were categorized into four groups according to vitamin D levels: patients with severe deficient (<10 ng/mL), deficient (10-19.9 ng/mL), insufficient (20-29.9 ng/mL) and sufficient (≥30 ng/mL) vitamin D levels. Among controls 49% individuals had subnormal vitamin D level. It was found that 91% of the CLD patients had subnormal vitamin-D levels. 20% of

CLD patients had vitamin D level less than 10 ng/mL i.e. severe vitamin D deficiency. Only 9% of CLD patients had sufficient vitamin D level.

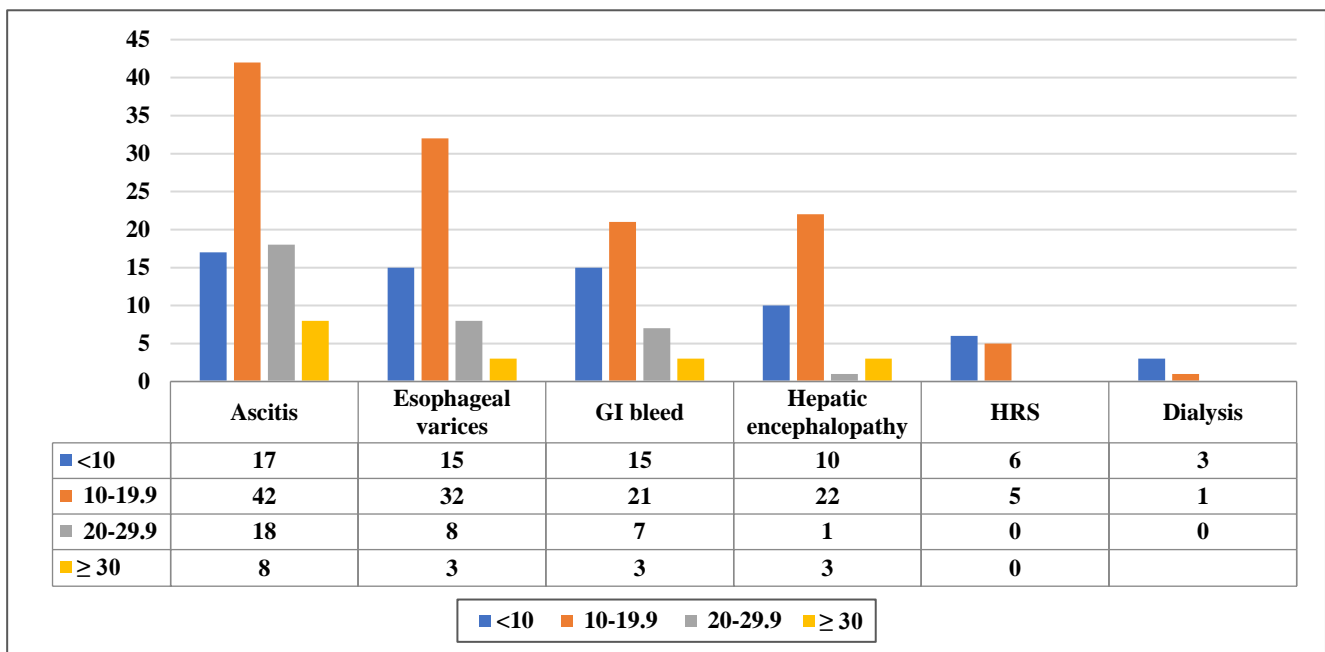


**Figure 6: Mean vitamin D level in various MELD-Na groups.**

The mean vitamin D level in control group was higher (30.12±6.60) than cases (15.97±7.45) (Table 10, Figure 15). The mean difference between case and control of Vitamin D were statistically significant with p<0.001.

The mean vitamin D level was 20.91±7.94 with Child-Pugh Class A (n=22), 16.43±7.00 with Child Pugh Class B (n=53) and 10.66±3.94 with Child-Pugh Class C (n=25). There was consistent trend towards lower vitamin D level with increasing severity of cirrhosis (p<0.001). Vitamin D level showed significant negative correlation with Child Pugh score (r= -0.446, p<0.001).

The mean vitamin D level was 19.89±8.64 with MELD-Na score ≤9 was found in 15 patients and as MELD-Na score increases mean vitamin D level become low. Low levels of vitamin D were significantly related with higher score of MELD-Na (p<0.001). Vitamin D level showed significant negative correlation with MELD-Na score (r=-0.395, p<0.001).



**Figure 7: Various observed complications in vitamin D level groups.**

Out of 100 cases, 92(92%) patients were discharged and death occurred in 8 (8%) patients. The mean vitamin D level was 9.61±3.01 in died patients and 16.52±7.47 in discharged patients. This shows low vitamin D level was associated with poor outcome. On applying unpaired T-test the difference of mean vitamin D level is statistically significant (p=0.011).

**DISCUSSION**

One-third of patients with liver cirrhosis suffer from vitamin D deficiency, and it results in hepatic osteodystrophy in these patients.<sup>13</sup> In this study, most of male patients belong to age group 31-50 years (n=44), young and middle age population, which is active and

productive mass of society. This is because alcoholism is common in this age group. Whereas most of the females was in age group 31-40 years, because autoimmune diseases commonly manifest in this age group. There is low prevalence of CLD in females in contrast to earlier study done by Putz-Bankuti et al, which consists of 51 males (68%) and 24 females (32%) with a mean age of 58±11 years (range: 25–89 years).<sup>13</sup> This is because of most of cases in this study belonged to alcoholic CLD and alcoholism is common in males but rare in females in our area. Comparatively lower age in this study is suggestive of growing problem of alcoholic liver disease.

The mean vitamin D level in cases (15.97±7.45) are lower than in controls (30.12±6.6). Subnormal vitamin D level

were seen in 91% of patients as compare to 52% in healthy individuals. Here we noted that there is significant magnitude of undiagnosed vitamin D inadequacy is prevalent in the healthy population in the community. Kumar et al found 46% of the normal population in northern India had vitamin D inadequacy.<sup>14</sup>

Zhao et al 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.<sup>15,16</sup> found that among 94 cirrhotic patients 87% had deficient levels of vitamin D. Kumar et al conducted a study on 160 cirrhotic patients in northern India and found inadequate levels of vitamin D in 80% of cirrhotic patients.<sup>14</sup> Similarly in this study vitamin D deficiency (<20 ng/dL) was found in 72 (72%) patients, out of them 20% suffered from severe vitamin D deficiency (<10 ng/dL). Vitamin D insufficiency (21-29.9 ng/dL) was found in 19 (19%). Thus, vitamin D levels were sub normal in 91 (91%) patients.

The mean level of vitamin D level in this study was  $15.97 \pm 7.45$  ng/mL. Putz-Bankuti et al did a study with 75 cirrhotic patients showing low serum Vitamin D levels of  $16.0 \pm 9.2$  ng/mL.<sup>17</sup>

Possible explanations of vitamin D deficiency in CLD could be because of decrease vitamin D hydroxylation and vitamin D binding protein (DBP) production, inadequate sun exposure, insufficient food intake, jaundice related deterioration of vitamin synthesis on the skin and decreased vitamin D absorption caused by intestinal edema secondary to portal hypertension or to cholestasis induced bile salt disruption.<sup>18,19</sup>

According to this study results, prevalence of deficiency and insufficiency increased with increasing Child-Pugh and MELD-Na scores. Child-Pugh class score C contains more number of vitamin-D deficient cases than class A or class B. A similar result was seen in a study by Fisher et al<sup>18</sup> in which vitamin-D deficient cases were highly found in class C. 20% of patients had vitamin D level less than 10 ng/mL with none in Child-Pugh stage A, 9% in Child-Pugh class B and 11% in Child-Pugh class C ( $p=0.001$ ) in this study.

The mean vitamin D level was 20.91 ng/mL with Child-Pugh Class A, 16.43 ng/mL with Child Pugh Class B and 10.66 ng/mL with Child-Pugh Class C; and there was consistent trend towards lower vitamin D level with increasing severity of cirrhosis ( $p<0.001$ ). On Linear regression analysis of vitamin D level we found significant negative correlation with Child-Pugh score ( $r=-0.446$ ,  $p<0.0001$ ) and MELD score ( $r=-0.395$ ,  $p<0.0001$ ). So low vitamin D levels were associated with increased severity of liver disease. Similar observations has been made by Miroliace et al, Putz-Bankuti et al and Finkelmeier et al.<sup>17,20,21</sup>

The association of vitamin D levels was also studied with different variables, as the secondary aim of the study. Vitamin D levels showed significant association with female sex ( $p=0.032$ ), serum bilirubin ( $p=0.002$ ) along with MELD-Na score ( $p=0.001$ ) and Child-Pugh score ( $p<0.0001$ ). But the similar association was not statistically significant with age, albumin, PT-INR, creatinine and sodium. Similarly in 180 patients with cirrhosis study done by Rech et al; they found no association of lower vitamin D level with increasing age and female sex but significant association with albumin, PT-INR, bilirubin and alcohol etiology.<sup>22</sup>

Finkelmeier et al reported that patients with severe 25(OH) D3 deficiency had the highest mortality risk (hazard ratio 2.225,  $p=0.002$ ).<sup>21</sup> These results suggest that vitamin D might be both a biomarker of severity and a potential therapeutic target in CLD. Similarly in this study low vitamin D level was significantly associated with occurrence of various complications of cirrhosis and poor outcome. Mean vitamin D level in patients with mortality was significantly lower (9.61 ng/mL) than in patients who discharged (16.52 ng/mL). This observation is further supported by the study done by Anty; who found the low vitamin D levels were associated with mortality; levels  $\leq 6$  ng/mL were associated with an unfavorable outcome and was an independent predictor for mortality.<sup>23</sup>

## CONCLUSION

In this study vitamin D insufficiency is highly prevalent in normal healthy population and patients with cirrhosis. Serum vitamin D levels are significantly lower in patients of liver cirrhosis than their healthy controls. Greater proportions of poor-prognostic liver disease patients have low vitamin-D levels.

The lower level of vitamin D is associated with severity of CLD and increased risk for complication and mortality. This study showed significant and inverse correlations between Vitamin D levels and MELD-Na score; and Child-Pugh score. Low vitamin-D levels could be a hindrance for the recovery of CLD patients.

The findings of the study suggest that awareness of serum vitamin-D level in patients with CLD is important. Vitamin D deficiency might be a valuable indicator of severity and predictor of mortality in cirrhosis patients. Measurement of vitamin D and replacement may be considered as part of the overall management of patients with cirrhosis of the liver as well as apparently healthy individuals.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*



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