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Correlation of Hypovitaminosis D with Decompensated Chronic Liver Disease: A Cross-Sectional Study

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Abstract: Hypovitaminosis D, an insufficiency or deficiency of vitamin D, can affect men and women across the lifespan. This fat-soluble vitamin affects mineral metabolism and numerous other physiologic functions. Chronic liver diseases (CLD) cause significant morbidity and mortality worldwide. The use of a biomarker such as 25-hydroxyvitamin D, indicates the severity of the disease, its complications and serves as a tool for early intervention. The present study was conducted with an objective to study the correlation of hypovitaminosis D in Decompensated Chronic Liver Disease and its clinical significance in Tertiary Care Hospital. The present study was an observational cross-sectional study carried out at the Department of Medicine of the tertiary care centre during November 2021 to October 2022. A total sample size of 60 patients with decompensated Chronic Liver Disease admitted in hospital was included in the study population. Vitamin D insufficiency is defined as 25 (OH) D level below 75 nmol/L (30 ng/mL) and deficiency as levels below 50 nmol/L (20 ng/mL). The outcome variables included levels of hypovitaminosis D in chronic liver disease patients, MELD score and Child Pugh Score. The statistical software namely SPSS 22.0 used for the analysis of the data. The mean age of the study population was 45.03 ±10.94 years. Majority of the patients were males (86.67%) Majority of patients with liver disease were with Vitamin D deficiency (76.67%) MELD score increases with vitamin deficiency and shows significant statistical association. The correlation of Vitamin D with MELD score and Child Pugh score shows significant strong negative correlation. This study was concluding that the Hypovitaminosis D is prevalent in chronic liver disease. CLD is associated with a significantly low level of vitamin D which was independent to gender.

Key Words: Correlation, Hypovitaminosis D, Decompensated Chronic Liver Disease, MELD Score, Child Pugh Score.

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1. INTRODUCTION

Vitamin D is a steroid hormone (secosteriod-where one of the bonds in the rings is broken). It has multiple effects and uses in the human body. The outcome of vitamin D deficiency in terms of osteoporosis, osteomalacia and increased fracture risk is well known.[1,2] Furthermore, the association between vitamin D deficiency and the development of infections, cardiovascular, autoimmune and degenerative diseases and several types of cancer (colon, prostate and breast cancer) has also been reported.[3] Chronic liver diseases (CLD) cause significant morbidity and mortality worldwide. Multiple etiological factors lead to a similar clinico-pathological syndrome in CLDs, although the rates of progression and clinical course may be different. Mortality data is most often used to assess the disease burden and there had been a 46% increase in CLD mortality in the world between 1980 to 2018, underscoring the emerging public health importance of CLD.[4,5] With the growing incidence of liver cirrhosis among Asians, the use of a biomarker such as 25-hydroxyvitamin D, indicates the severity of the disease, its complications and serves as a tool for early intervention. [5] Vitamin D insufficiency and deficiency are prevalent in almost half the healthy population of developed countries.[6] Most experts define vitamin D insufficiency as a 25(OH)D level below 75 nmol/L (30 ng/mL) and deficiency as levels below 50 nmol/L (20 ng/mL). It is estimated that one billion people suffer from deficiency or insufficiency of vitamin D.[7] In the United States, between 25% and 50% of the adult population has vitamin D deficiency.[8] In patients with chronic liver diseases, the prevalence of vitamin D deficits is much higher and practically universal. [9] Up to 93% of patients with chronic liver disease have insufficient vitamin D levels, and almost one-third of these show severe deficiency.[5] The majority of the studies on patients with cirrhosis confirm the prevalence of vitamin D deficiency in this setting. The question of whether liver damage precipitates the disturbance in vitamin D homeostasis or the other way around, still remains, leading to a type of "chicken or the egg" causality dilemma. However, whatever its role in liver disease (epiphenomenon of cirrhosis or co-factor of liver fibrosis and necroinflammation), vitamin D must still be considered as a diagnostic tool and prognostic index.[10] Therefore, the primary aim of this study was to document vitamin D deficiency in patients with chronic liver disease and to study the correlation of hypovitaminosis D in Decompensated Chronic Liver Disease and its clinical significance. Our objective to achieve our aim, is to estimate Vit-25(OH)D level in patients with chronic liver disease and to compare of Mean Value of Vitamin D Level in Relation to MELD Score and Child Pugh Score.

2. METHODOLOGY

The present study was an observational cross-sectional study carried out at the Department of Medicine of tertiary care centres during November 2021 to October 2022. The study was conducted after obtaining clearance from the Ethical Committee of the institute.

2.1. Hypovitaminosis Levels

- Optimal vitamin – 30 to 50 ng/mL (i.e. 75-125 nmol/L)
- Vitamin D deficiency - lower than 20 ng/mL (i.e. 50 nmol/L)
- Vitamin D insufficiency-between 20 and 30 ng/mL (i.e. 50-75nmol/L)

2.2. Sample Size

A total sample size of 60 patients with decompensated Chronic Liver Disease admitted in hospital was included in the study population and has been calculated using R statistical software with 95% of confidence interval and 80% of the power. The study subjects were chosen as per the inclusion and exclusion criteria

2.3. Inclusion Criteria

- Patients over 18 years
- Patients who have chronic liver disease as per operational definition.

2.4. Exclusion Critetia

- Chronic renal failure
- Pregnancy and breastfeeding
- Granulomatous disease

2.5. Operational Definitions

Chronic Liver Disease – Progressive destruction of the liver parenchyma over a period greater than 6 months.

2.6. Study procedure

All the participants were selected as per inclusion and exclusion critetia. Chronic Liver Disease is defined as progressive destruction of the liver parenchyma over a period greater than 6 Months. A detailed demographic credentials, complete history and clinical examination of the patients was done and recorded using pre designed proforma. History of alcohol intake and dependency was assessed by CAGE questionnaire. The patients who are diagnosed as CLD was categorized based on aetiology as alcoholic, non-alcoholic, infective and autoimmune. Serum vitamin D level was measured by ELISA in those patients.

2.7. Ethical Statement

Written informed consent was obtained from all the study participants after getting approval from the institutional ethical committee with reference number MC/Ethics 2022/59 dated 14/03/2022.

3. RESULTS

Table 1: Demographic profile among cases

Demographic profile		No. of Patients (n=97)	Percentage
Age group (years)	21-30	05	08.33
	31-40	25	41.67
	40-50	11	18.33

	51-60	13	21.67
	61-70	04	06.67
	>70	02	03.33
Gender	Male	52	86.67
	Female	08	13.33

The table no. 1 describes the demographic profile of the patients. Majority of patients were in the age group 31-40 years. (41.67%) The mean age of the study population was 45.03 ±10.94 years. Majority of the patients were males (86.67%)

Table 2: Distribution according to Vitamin D levels

Vitamin D levels	Frequency	Total
Optimal (>30-50)	00	00.00
Insufficiency (20-30)	14	23.33
Deficiency (<20)	46	76.67
Total	60	100

It was seen that according to vitamin D levels the majority of patients with liver disease were with Vitamin D deficiency (76.67%) while insufficiency of vitamin D was observed in 14 (23.33%) patients.

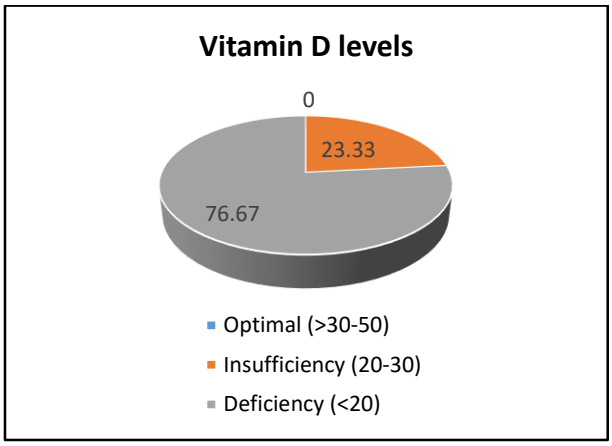

Fig 1: Distribution according to Vitamin D levels

Table 3: Association of MELD score and Vitamin D levels

Vitamin D levels (ng/mL)	n	MELD (Mean ±SD)	P value
Insufficiency (20-30)	14	17.28 ±5.22	0.03 (S)
Deficiency (<20)	46	22.29 ±7.11	

It was seen that patients with Vitamin D deficiency had mean MELD score of 22.29±7.11 as compared to 17.28±5.22 among patients with insufficiency of vitamin D. This shows that MELD score increases with vitamin deficiency and shows significant statistical association. (P<0.05, by unpaired t test)

Table 4: Association of CHILD PUGH score and Vitamin D levels

Vitamin D levels	n	CHILD PUGH score (Mean ±SD)	P value
Insufficiency (20-30)	14	11.78 ±6.18	0.04 (S)
Deficiency (<20)	46	12.08 ±5.07	

It was seen that patients with Vitamin D deficiency had mean CHILD PUGH score of 12.08 ±5.07 as compared to 12.08 ±5.07 among patients with insufficiency of vitamin D. This shows that CHILD PUGH score increases with vitamin deficiency and shows significant statistical association. (P<0.05, by unpaired t test)

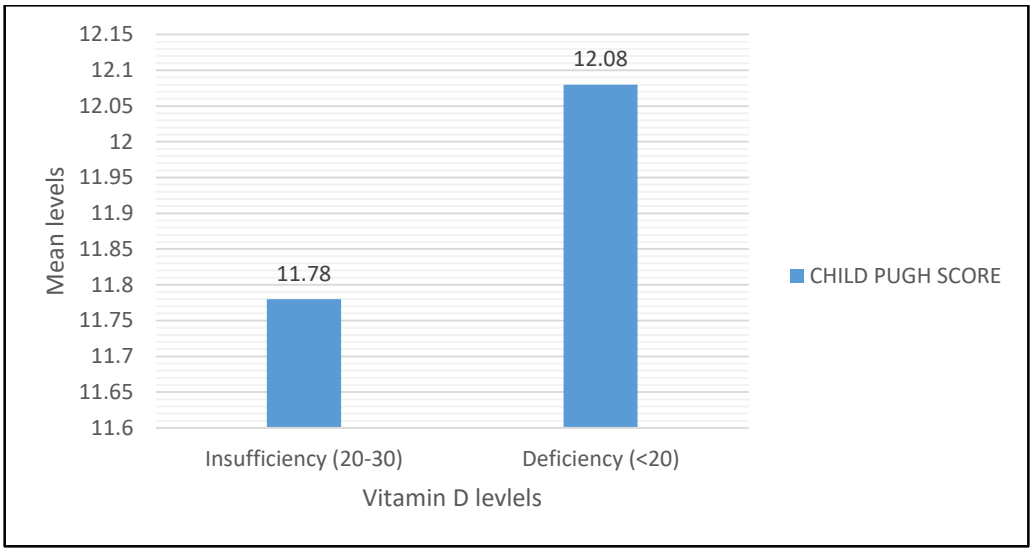

Fig 2: Association of Child Pugh score and Vitamin D levels

Table 5: Association of CHILD PUGH score and Vitamin D levels

CHILD PUGH score	Vitamin D levels		Total
	Insufficiency (20-30 ng/mL)	Deficiency (<20 ng/mL)	
A	04	01	05
B	06	20	26
C	04	25	29
Total	14	46	60

It was seen that patients with Vitamin D deficiency had CHILD PUGH score C among 4 (28.57%) patients as compared to 25 (54.35%) patients among patients with insufficiency of vitamin D. This shows that CHILD PUGH score increases with vitamin deficiency and shows significant statistical association. (P<0.05, by chi-square test)

Table 6: Correlation of Vitamin D levels with CHILD PUGH score and MELD score

Correlation	Pearsons's coefficient (r)	P value
Vit D vs CHILD PUGH	-0.342	<0.0001 (S)
Vit D vs MELD score	-0.419	<0.0001 (S)

It was seen that correlation of Vitamin D and CHILD PUGH score shows significant strong negative correlation. (-0.342) This shows that CHILD PUGH score increases as vitamin D levels decrease with significant statistical difference (P<0.05, by Pearsons's correlation test). It was seen that correlation of Vitamin D and MELD score shows significant strong negative correlation. (r=-0.419) This shows that MELD score increases as vitamin D levels decrease with significant statistical difference (P<0.05, by Pearsons's correlation test)

4. DISCUSSION

Vitamin D deficiency has been frequently reported in many causes of chronic liver disease. The involvement of vitamin D in the activation and regulation of both innate and adaptive immune systems and its antiproliferative effect may explain its importance in liver diseases.[2,3] The present observational cross-sectional study was conducted in the tertiary care institute with the aim to evaluate the levels of vitamin D in Patients of decompensated chronic liver disease and look for hypovitaminosis.

4.1. Age

In the present study, it was seen that the majority of the patients in the present study were 31-40 years of age. (41.67%) The mean age of the study population was 45.03 ±10.94 yrs. Arteh J et al [5] in a study on prevalence of vitamin D deficiency in patients with chronic liver disease observed the mean age of the patients was 53 ± 9 years. This finding was similar to the present study. Gupta BK et al [11] in a study observed mean age was 46 ±10 (males) and 45±19 (females). Silva MC et al [12] investigated the prevalence of hypovitaminosis D in liver disease and observed the mean age was 53.9 ± 12.1 years among patients. Sharma et.al.[14] the mean age of the study population was 41.83±10.36 (18-59) years

4.2. Gender

There was predominance of the male gender (72.2%) and of which it was seen that majority of the patients were male (86.67%) with 6.5:1 of male: female proportion. Gupta BK et al [11] in a study observed out of 100 patients, 91 (91%) were males and remaining 9 (9%) were females. Arora I et al [13] observed a total of 157 (134 males and 23 female) patients of chronic liver disease. Arteh J et al [5] in a study consisted of 59 males and 59 females.

4.3. Distribution of Vitamin D Deficiency

In the present study, it was seen that according to vitamin D levels the majority of patients with liver disease were with Vitamin D deficiency (76.67%) while insufficiency of vitamin D was observed in 14 (23.33%) patients. No patients were with normal vitamin D levels. Arteh J et al [5] observed Vitamin D deficiency, was seen in 109 out of 118 patients (92.4%). Gupta BK et al[11] observed prevalence of vitamin D deficiency and insufficiency were 43% and 42% respectively among CLD patients. Sharma et. al.[14] Vitamin D level was found to be Deficient (≤20 ng/ml) among 32 (32.0%), Insufficient (20-30 ng/ml) among 26 (26.0%) and Optimum (> 30 ng/ml) among 42 (42.0%) subjects. Arora I et al [13] in a study observed Vitamin D deficiency and insufficiency was found in 87.63% and 10.3%, respectively. One mechanism for the higher prevalence of vitamin D deficiency in cirrhotics is impairment in the 25-hydroxylation of vitamin D [2, 10] which occurs in cholestatic forms of liver disease and alcoholic cirrhosis and leads to low serum levels of 25(OH)D in relation to the degree of liver dysfunction. In the present study, MELD score increases with vitamin deficiency and shows significant statistical association. The correlation of Vitamin D and MELD score shows significant strong negative correlation. (r=-0.419). Gupta BK et al [11] in a study observed low levels of vitamin D were significantly related with higher score of MELD ($p<0.05$) This finding was similar to the present study. Silva MC et al [12] observed admission for acute decompensation of liver disease was also associated with higher MELD score. In the present study, CHILD PUGH score increases with vitamin deficiency and shows significant statistical association. ($P<0.05$, by unpaired t test). Arora I et al [13] observed Child A category had a smaller number of patients with vitamin D deficiency as compared to Child B and Child C (P- value<0.02). This finding was similar to present study. It was seen that correlation of Vitamin D and CHILD PUGH score shows significant strong negative correlation. (-0.342). Gupta BK et al[11] in a study observed there was consistent trend towards lower vitamin D level with increasing severity of cirrhosis. On Linear regression vitamin D level showed significant negative correlation with Child Pugh score ($r= –0.7382$, $p<0.0001$). Silva MC et al [12] investigated the prevalence of hypovitaminosis D and the factors related to its occurrence observed there were no significant differences in 25(OH)D levels when Child-Pugh C patients were compared to the remaining subjects ($P = 0.243$). Kumar et. al.[15] investigated the prevalence of 89% who had insufficiency or deficiency of vitamin D in their serum with the majority having moderate to severe grades of CLD as per CP score. This association was statistically significant with p value of less than <0.01. Also, a negative Pearson correlation was observed meaning thereby that as the CP score increases, the vitamin D levels decrease. CLD is associated with a significantly low level of vitamin D and lower level of vitamin D is associated with severity of CLD. One of the limitations of the study is that we did not measure parathyroid hormone (PTH) levels and hence we could not further explore the interaction between PTH levels and vitamin D calcium levels in liver disease, especially in those with advanced liver disease.

5. CONCLUSION

The present study concludes that hypovitaminosis D was prevalent in chronic liver disease. This study observe negative correlation between vitamin D and CLD. CLD is associated with a significantly low level of vitamin D which is independent of gender, BMI, residence and education level. The lower level of vitamin D is associated with severity of CLD. Despite the cross sectional design and limited sample size there is exists a strong contribution of vitamin D deficiency in the worsening of liver disease, so further intervational studies by pre and post vitamin D supplementation of CLD patients will help in treating these CLD patients in future.

6. AUTHORS CONTRIBUTION STATEMENT

Dr. Gurkirat Arora gathered the data with regard to this study. Dr. D. P. Lakra and Dr. R. K. Patel conceptualized and necessary inputs were given towards the designing of the study. Dr. C. S. Sharma and Dr. Gurkirat Arora analysed these data. All authors discussed the methodology and results and contributed to the final manuscript.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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