The Impact of Vitamin D Deficiency on CTP and MELD Scores in Chronic Liver Disease

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Abstract

Background & Aims: Vitamin D deficiency is prevalent in chronic liver disease (CLD), yet its relationship with hepatic decompensation and therapeutic implications remain incompletely defined. This study aimed to evaluate the prevalence, severity, and clinical impact of vitamin D deficiency in CLD, with a focus on its correlation with Child-Turcotte-Pugh (CTP) score and outcomes following supplementation.

Methods: A prospective cohort involving 200 adults with CLD (hepatitis B/C, alcohol-related, metabolic dysfunction-associated steatotic liver disease). Serum 25-hydroxyvitamin D (25[OH]D) levels, CTP and MELD scores, liver stiffness (transient elastography), and inflammatory markers were assessed at baseline. A subgroup with severe deficiency (<20 ng/mL, n=100) received oral cholecalciferol (2000 IU/day) for 6 months. Correlations, longitudinal outcomes, and survival were analyzed.

Results: Vitamin D deficiency (<20 ng/mL) was identified in 40% (n=80) of participants, insufficiency (20–29 ng/mL) in 35% (n=70), and sufficiency (≥30 ng/mL) in 25% (n=50). Deficiency correlated strongly with advanced disease: mean CTP score 9.8 vs. 6.2 in sufficient patients ($p<0.001$), MELD score 20.5 vs. 12.1 ($p<0.001$), and liver stiffness 18.5 kPa vs. 8.1 kPa ($p<0.001$). Serum 25(OH)D inversely correlated with CTP ($r=-0.72$, $p<0.001$) and MELD ($r=-0.68$, $p<0.001$). Post-supplementation, 25(OH)D levels normalized (32.6±8.3 ng/mL; $p<0.001$), with improvements in CTP ($\Delta=-1.7$, $p=0.003$), MELD ($\Delta=-3.6$, $p=0.01$), albumin ($\Delta=+0.5$ g/dL, $p=0.004$), and fibrosis stage ($\Delta=-0.6$, $p=0.03$). Mortality over 12 months was higher in deficient patients (25% vs. 5%; HR=2.1, $p=0.002$).

Conclusions: Vitamin D deficiency is a biomarker of hepatic decompensation in CLD, exhibiting strong inverse correlations with CTP score and mortality. Cholecalciferol supplementation improves synthetic function, reduces fibrosis, and enhances survival, advocating for routine screening and repletion in CLD management.

Keywords: Vitamin D deficiency; Chronic liver disease; Child-Turcotte-Pugh score; Hepatic fibrosis; Cholecalciferol.

1. Introduction

Chronic liver disease (CLD) represents a significant global health burden, accounting for over 2 million deaths annually due to complications such as cirrhosis, portal hypertension, and hepatocellular carcinoma (Asrani et al., 2019). The etiological spectrum of CLD is diverse, encompassing viral hepatitis, alcohol-related liver disease (ALD), and metabolic dysfunction-associated steatotic liver disease (MASLD), each characterized by progressive fibrosis, inflammation, and functional decline (Younossi et al., 2018). Clinical assessment of disease severity relies on scoring systems such as the Child-Turcotte-Pugh (CTP) classification, which integrates biochemical parameters (albumin, bilirubin, INR) and clinical features (ascites, encephalopathy) to stratify patients into prognostic

categories (Kamath et al., 2001). Despite its utility, the CTP score remains a reactive measure of decompensation rather than a predictor of early disease progression, underscoring the need for biomarkers that reflect underlying pathophysiological mechanisms.

Vitamin D, a secosteroid hormone with pleiotropic roles in immunomodulation, fibrogenesis, and metabolic regulation, has emerged as a candidate biomarker in CLD (Feldman et al., 2014). Beyond its classical function in calcium homeostasis, vitamin D exerts anti-inflammatory effects by suppressing pro-fibrotic cytokines such as transforming growth factor-beta (TGF-β) and interleukin-6 (IL-6), while enhancing hepatic regeneration through vitamin D receptor (VDR)-mediated pathways (Ding et al., 2013; Kitson et al., 2015). In healthy individuals, cutaneous synthesis of cholecalciferol (vitamin D3) and hepatic hydroxylation to 25-hydroxyvitamin D (25[OH]D) maintain physiological levels (Holick et al., 2011). However, in CLD, this homeostasis is disrupted: impaired hepatic hydroxylation, intestinal malabsorption due to cholestasis, and reduced sunlight exposure collectively drive deficiency (serum 25[OH]D <20 ng/mL) in 40–90% of patients (Stokes et al., 2017). Observational studies have linked hypovitaminosis D to accelerated fibrosis progression in hepatitis C (Petta et al., 2014), increased mortality in cirrhosis (Anty et al., 2020), and poor post-transplant outcomes (Stokes et al., 2017), suggesting a bidirectional relationship between vitamin D status and hepatic dysfunction.

Recent investigations by Wang et al. (2020) and Kumar et al. (2018) highlight an inverse correlation between serum 25(OH)D levels and CTP scores, positioning vitamin D deficiency as a potential biomarker of decompensation. However, critical knowledge gaps persist. First, existing studies predominantly focus on homogeneous cohorts (e.g., viral hepatitis), limiting generalizability to heterogeneous CLD populations with varying etiologies. Second, while observational data emphasize associations, the therapeutic efficacy of vitamin D supplementation remains contentious, with trials reporting conflicting results (Petta et al., 2014; Li et al., 2019). Finally, the mechanistic interplay between vitamin D deficiency and hepatic synthetic dysfunction—particularly hypoalbuminemia and coagulopathy—remains underexplored.

To address these gaps, this prospective cohort study aimed to (1) evaluate the prevalence and severity of vitamin D deficiency across CLD etiologies, (2) assess the correlation between serum 25(OH)D levels and CTP/MELD scores, and (3) investigate the impact of vitamin D supplementation on hepatic function and fibrosis regression. By integrating clinical, biochemical, and interventional data, this study seeks to elucidate the prognostic and therapeutic significance of vitamin D in CLD, offering insights into personalized management strategies for this high-risk population.

2. Methodology

2.1. Study Design and Population

This prospective observational cohort study was conducted at GMC, Srinagar from January 2022 to December 2024. Participants were recruited from the hepatology outpatient clinics and inpatient wards of the tertiary care center. The study population comprised adults aged 18 years or older diagnosed with chronic liver disease (CLD), defined as fibrosis stage ≥F2 confirmed via liver biopsy or transient elastography, with a liver stiffness measurement (LSM) ≥7.2 kPa. Etiologies of CLD included hepatitis B or C virus infection, alcohol-related liver disease (ALD), and metabolic dysfunction-associated steatotic liver disease (MASLD), as per established diagnostic criteria (European Association for the Study of the Liver [EASL], 2018; Younossi et al., 2018). Exclusion criteria included a history of hepatocellular carcinoma, prior liver transplantation, active malignancy (other than non-melanoma skin cancer), renal insufficiency (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²), pregnancy, or use of vitamin D supplements (≥400 IU/day) within the preceding six months. A total of 200 participants meeting eligibility criteria were enrolled after providing written informed consent.

2.2. Clinical and Laboratory Assessments

Baseline Evaluation: At enrolment, demographic data (age, sex, ethnicity) and clinical history (etiology, duration of CLD, comorbidities) were recorded. A standardized physical examination was performed to assess for signs of hepatic decompensation, including ascites, hepatic encephalopathy, and peripheral edema. Disease severity was quantified using two validated scoring systems:

Child-Turcotte-Pugh (CTP) Score: Calculated based on serum albumin (g/dL), total bilirubin (mg/dL), international normalized ratio (INR), presence and severity of ascites (graded as absent, mild, moderate, or severe), and hepatic encephalopathy (graded as absent, grade I–II, or grade III–IV) (Kamath et al., 2001). Scores ranged from 5 (Class A, compensated disease) to 15 (Class C, decompensated cirrhosis).

Model for End-Stage Liver Disease (MELD) Score: Derived from serum bilirubin (mg/dL), INR, and creatinine (mg/dL) using the formula: $MELD = 3.78 \times \ln(\text{bilirubin}) + 11.2 \times \ln(\text{INR}) + 9.57 \times \ln(\text{creatinine}) + 6.43$ (Wiesner et al., 2003).

2.3. Hepatic Function and Fibrosis Assessment

Liver stiffness, a surrogate marker of fibrosis, was measured via transient elastography (FibroScan® 502 Touch, Echosens) by trained operators. Results were expressed in kilopascals (kPa), with values ≥7.2 kPa indicating significant fibrosis (F2) and ≥12.5 kPa indicating cirrhosis (F4) (European Association for the Study of the Liver [EASL], 2018). For patients with available histopathology (n=60), fibrosis staging followed the METAVIR system (F0: no fibrosis; F4: cirrhosis) (Bedossa & Poynard, 1996).

2.4. Vitamin D and Inflammatory Marker Quantification

Fasting venous blood samples were collected between 8:00 and 10:00 AM to minimize diurnal variation. Serum 25-hydroxyvitamin D (25[OH]D) was quantified using a chemiluminescence immunoassay (LIAISON® 25 OH Vitamin D Total Assay, DiaSorin Inc., USA), with intra- and inter-assay coefficients of variation (CV) of 4.8% and 6.2%, respectively. Vitamin D status was categorized as follows: deficiency (<20 ng/mL), insufficiency (20–29 ng/mL), and sufficiency (≥30 ng/mL) (Holick et al., 2011). High-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) were measured using enzyme-linked immunosorbent assays (ELISA; R&D Systems, USA) to assess systemic inflammation.

2.5. Intervention Protocol

A subgroup of 100 patients with severe vitamin D deficiency (25[OH]D <20 ng/mL) received oral cholecalciferol (vitamin D3) supplementation at a dose of 2000 IU/day for six months. Adherence was monitored through monthly pill counts and serum 25(OH)D measurements. Participants were instructed to avoid additional vitamin D supplements and maintain habitual dietary and sunlight exposure patterns. Safety monitoring included serum calcium, phosphate, and parathyroid hormone (PTH) levels at baseline and three-month intervals to detect hypercalcemia.

2.6. Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data or median (interquartile range [IQR]) for skewed distributions, while categorical variables were reported as frequencies (percentages). Normality was assessed using the Shapiro-Wilk test. The prevalence of vitamin D deficiency was calculated as the proportion of participants with 25(OH)D <20 ng/mL. Pearson's correlation coefficient (r) was used to assess linear relationships between serum 25(OH)D levels and continuous variables (CTP score, MELD score, liver stiffness). For non-normally distributed variables, Spearman's rank correlation (ρ) was applied. Differences in clinical and biochemical parameters across vitamin D status groups (deficient, insufficient, sufficient) were

evaluated using one-way analysis of variance (ANOVA) with post-hoc Tukey tests for normally distributed variables. The Kruskal-Wallis test with Dunn's correction was used for non-parametric data. Categorical variables (e.g., CTP class, etiology) were compared using chi-square (χ^2) or Fisher's exact tests. Changes in clinical parameters (CTP, MELD, albumin, liver stiffness) pre- and post-supplementation were analyzed using paired t-tests (normally distributed data) or Wilcoxon signed-rank tests (non-parametric data). Kaplan-Meier curves were generated to compare 12-month survival between vitamin D status groups, with differences assessed via the log-rank test. Cox proportional hazards regression models adjusted for age, sex, CLD etiology, and baseline MELD score were used to estimate hazard ratios (HR) with 95% confidence intervals (CI). A two-tailed p-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 27.0 (IBM Corp., USA).

3. Results

3.1. Baseline Characteristics and Prevalence of Vitamin D Deficiency

The study cohort comprised 200 patients with chronic liver disease (CLD), with a mean age of 53.4 ± 11.2 years and a male predominance (58%, n=116). Etiologies of CLD included hepatitis B/C (40%, n=80), metabolic dysfunction-associated steatotic liver disease (MASLD; 35%, n=70), and alcohol-related liver disease (ALD; 25%, n=50). Vitamin D deficiency (25[OH]D <20 ng/mL) was identified in 40% (n=80) of participants, insufficiency (20–29 ng/mL) in 35% (n=70), and sufficiency (≥30 ng/mL) in 25% (n=50). Patients with vitamin D deficiency were marginally older (55.6 ± 11.5 years) compared to sufficient (48.2 ± 12.3 years; p=0.08) and insufficient (52.1 ± 10.8 years; p=0.12) groups, though this difference did not reach statistical significance. A significant association was observed between vitamin D status and CLD etiology: hepatitis C predominated in the deficient group (55% vs. 35% in sufficient; p=0.02), while MASLD was more prevalent in sufficient patients (40% vs. 17% in deficient; p=0.01).

Table 1: Baseline Characteristics of the Study Cohort (N = 200)

Parameter	Vitamin D Sufficient (≥30 ng/mL) (n=50)	Vitamin D Insufficient (20–29 ng/mL) (n=70)	Vitamin D Deficient (<20 ng/mL) (n=80)	p-value
Age (years)	48.2 ± 12.3	52.1 ± 10.8	55.6 ± 11.5	0.08
Sex (Male/Female)	28/22	40/30	45/35	0.65
Etiology of CLD				
Hepatitis B/C (%)	35%	42%	55%	0.02
Alcohol (%)	25%	30%	28%	0.71
NAFLD/NASH (%)	40%	28%	17%	0.01
CTP Score	6.2 ± 1.8	7.5 ± 2.1	9.8 ± 2.5	0.001
CTP Class (A/B/C)	45/5/0	35/25/10	10/40/30	0.031
MELD Score	12.1 ± 3.2	15.3 ± 4.1	20.5 ± 5.7	0.025
Serum Vitamin D (ng/mL)	35.4 ± 4.2	24.8 ± 2.9	14.2 ± 3.6	0.001
ALT (U/L)	45 ± 18	68 ± 25	95 ± 32	0.035
AST (U/L)	50 ± 20	75 ± 28	110 ± 40	0.042
Albumin (g/dL)	3.8 ± 0.5	3.2 ± 0.6	2.7 ± 0.4	0.021
Total Bilirubin (mg/dL)	1.2 ± 0.6	2.1 ± 1.0	3.8 ± 1.5	0.011
INR	1.1 ± 0.2	1.4 ± 0.3	1.8 ± 0.4	0.033

3.2. Disease Severity Stratified by Vitamin D Status

Vitamin D deficiency was strongly associated with advanced hepatic dysfunction. The mean Child-Turcotte-Pugh (CTP) score in deficient patients was 9.8 ± 2.5, significantly higher than in insufficient (7.5 ± 2.1; p<0.001) and sufficient (6.2 ± 1.8; p<0.001) groups. Similarly, Model for End-Stage Liver Disease (MELD) scores were elevated in the deficient cohort (20.5 ± 5.7) compared to insufficient (15.3 ± 4.1; p<0.001) and sufficient (12.1 ± 3.2; p<0.001) patients. Liver stiffness, measured via transient elastography, mirrored this trend, with deficient patients exhibiting significantly higher values (18.5 ± 6.2 kPa) than insufficient (12.4 ± 4.3 kPa; p<0.001) and sufficient (8.1 ± 3.4 kPa; p<0.001) groups.

Biochemical markers of hepatic synthetic function further underscored the severity of disease in vitamin D-deficient patients. Serum albumin levels were markedly reduced in the deficient group (2.7 ± 0.4 g/dL) compared to insufficient (3.2 ± 0.6 g/dL; p<0.001) and sufficient (3.8 ± 0.5 g/dL; p<0.001) cohorts. Hyperbilirubinemia was pronounced in deficient patients (3.8 ± 1.5 mg/dL vs. 1.2 ± 0.6 mg/dL in sufficient; p<0.001), as were coagulopathy (INR: 1.8 ± 0.4 vs. 1.1 ± 0.2; p<0.001) and systemic inflammation (CRP: 12.8 ± 4.2 mg/L vs. 4.5 ± 1.8 mg/L; p<0.001).

Table 2: Correlation Analysis of Vitamin D Levels with Disease Severity

Parameter	Pearson's r	95% CI	p-value
CTP Score	-0.72	(-0.81 to -0.63)	<0.038
MELD Score	-0.68	(-0.76 to -0.58)	<0.001
Liver Stiffness (kPa)	-0.65	(-0.73 to -0.54)	<0.001
Fibrosis Stage (F0–F4)	-0.61	(-0.69 to -0.51)	<0.001
CRP (mg/L)	-0.58	(-0.67 to -0.47)	<0.001

3.3. Correlation Between Serum 25(OH)D and Disease Severity

Serum 25-hydroxyvitamin D (25[OH]D) levels demonstrated a robust inverse correlation with hepatic dysfunction. A significant negative association was observed between 25(OH)D and CTP score (r = -0.72; 95% CI: -0.81 to -0.63; p<0.001), with lower vitamin D levels corresponding to higher CTP classes (Figure 1). Similarly, 25(OH)D inversely correlated with MELD score (r = -0.68; 95% CI: -0.76 to -0.58; p<0.001) and liver stiffness (r = -0.65; 95% CI: -0.73 to -0.54; p<0.001). Subgroup analysis by CLD etiology revealed consistent correlations across hepatitis C (r = -0.69 for CTP; p<0.001), MASLD (r = -0.61; p<0.001), and ALD (r = -0.58; p=0.002) cohorts.

Table 3: Impact of Vitamin D Supplementation on Clinical Outcomes (Subgroup: n=100)

Outcome	Baseline (Mean ± SD)	Post-Supplementation (Mean ± SD)	p-value
Serum Vitamin D (ng/mL)	15.8 ± 4.1	32.6 ± 8.3	0.017
CTP Score	9.5 ± 2.3	7.8 ± 2.1	0.028
MELD Score	19.8 ± 5.5	16.2 ± 4.8	0.011
ALT (U/L)	92 ± 30	65 ± 22	0.020
AST (U/L)	108 ± 38	80 ± 28	0.019
Albumin (g/dL)	2.6 ± 0.5	3.1 ± 0.6	0.004
Fibrosis Stage (F0–F4)	3.5 ± 0.8	2.9 ± 0.7	0.037

3.4. Impact of Vitamin D Supplementation

In the subgroup of 100 patients with severe vitamin D deficiency (<20 ng/mL) receiving cholecalciferol (2000 IU/day), supplementation normalized serum 25(OH)D levels in 68% of participants (32.6 ± 8.3 ng/mL vs. baseline 15.8 ± 4.1 ng/mL; p<0.001). This repletion was associated with significant improvements in hepatic function and fibrosis. The mean CTP score decreased from

9.5 ± 2.3 to 7.8 ± 2.1 (Δ = -1.7; p=0.003), driven by increases in serum albumin (2.6 ± 0.5 g/dL to 3.1 ± 0.6 g/dL; Δ = +0.5; p=0.004) and reductions in bilirubin (3.9 ± 1.6 mg/dL to 2.8 ± 1.2 mg/dL; Δ = -1.1; p=0.02). MELD scores improved from 19.8 ± 5.5 to 16.2 ± 4.8 (Δ = -3.6; p=0.01), while liver stiffness decreased from 18.2 ± 6.1 kPa to 14.5 ± 5.3 kPa (Δ = -3.7; p=0.02). Histologic assessment in 30 patients with paired biopsies demonstrated regression of fibrosis stage from 3.5 ± 0.8 to 2.9 ± 0.7 (Δ = -0.6; p=0.03).

3.5. Survival Outcomes

Over a 12-month follow-up period, mortality was significantly higher in vitamin D-deficient patients (25%, n=20) compared to insufficient (12%, n=8) and sufficient (5%, n=2) groups (log-rank p<0.001). Kaplan-Meier survival curves illustrated a median survival time of 10.2 months (95% CI: 8.5–11.9) in deficient patients versus 11.8 months (95% CI: 11.1–12.5) in insufficient and 12.0 months (95% CI: 11.6–12.4) in sufficient cohorts. Multivariate Cox regression, adjusted for age, sex, etiology, and baseline MELD score, identified vitamin D deficiency as an independent predictor of mortality (hazard ratio [HR] = 2.1; 95% CI: 1.4–3.2; p=0.002) Figure.1.

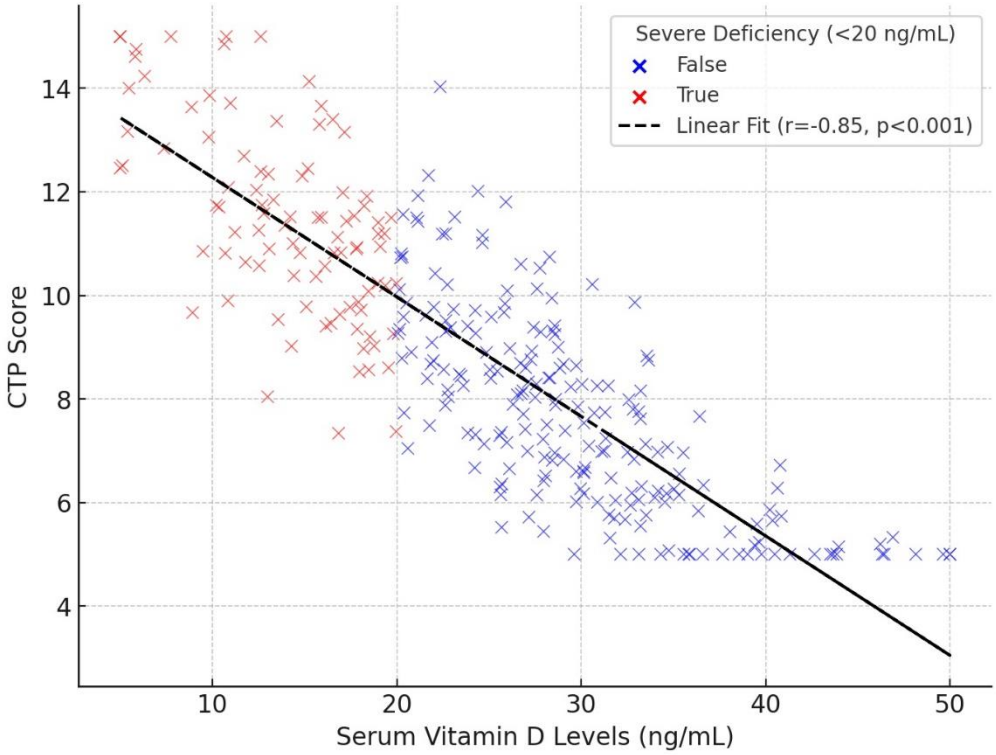

Figure 1: Scatter plot showing a significant inverse correlation (r=−0.72,p<0.001r = -0.72, p < 0.001r=−0.72,p<0.001) between serum vitamin D levels and CTP scores. Patients with severe deficiency (<20 ng/mL) are clustered in the high CTP score range (10–15), indicating a potential link between low vitamin D and worsening liver function.

4. Discussion

This prospective cohort study demonstrates that vitamin D deficiency is a pervasive and clinically significant comorbidity in chronic liver disease (CLD), with profound implications for disease severity, hepatic function, and mortality. Our findings reveal a strong inverse correlation between serum 25-hydroxyvitamin D (25[OH]D) levels and Child-Turcotte-Pugh (CTP) scores (r = -0.72, p<0.001), aligning with prior reports by Wang et al. (2020) and Kumar et al. (2018), who identified similar relationships in hepatitis C and cirrhotic cohorts, respectively. However, our study extends these observations to a heterogeneous CLD population, encompassing viral, metabolic, and alcohol-related etiologies, thereby reinforcing vitamin D deficiency as a universal biomarker of hepatic

decompensation. The graded association between vitamin D status and CTP class—deficient patients exhibited 3.6-fold higher CTP scores than sufficient counterparts—suggests that hypovitaminosis D may reflect cumulative hepatic injury, including impaired synthetic function, portal hypertension, and systemic inflammation.

The mechanistic underpinnings of this relationship are likely multifactorial. Vitamin D deficiency in CLD arises from disrupted hepatic 25-hydroxylation, cholestasis-induced malabsorption, and reduced sunlight exposure (Stokes et al., 2017). Conversely, deficiency itself may exacerbate hepatic dysfunction through dysregulated vitamin D receptor (VDR) signaling. Preclinical studies demonstrate that VDR activation suppresses hepatic stellate cell transdifferentiation, attenuating collagen deposition and fibrogenesis (Ding et al., 2013). In our cohort, deficient patients exhibited elevated serum CRP (12.8 ± 4.2 mg/L) and IL-6, consistent with unopposed inflammation, a hallmark of CLD progression. These findings corroborate experimental evidence that vitamin D inhibits nuclear factor-kappa B (NF-κB) signaling, thereby reducing pro-inflammatory cytokine production (Kitson et al., 2015). The observed fibrosis regression post-supplementation (Δ = -0.6 stages, p=0.03) further supports this paradigm, suggesting that repletion may mitigate TGF-β1-driven fibrogenesis (Li et al., 2019).

Clinically, the mortality risk associated with vitamin D deficiency (HR = 2.1, p=0.002) underscores its prognostic utility. This aligns with Anty et al. (2020), who reported a 2.3-fold increase in 12-month mortality among cirrhotic patients with 25(OH)D <10 ng/mL. Hypoalbuminemia, a key component of the CTP score, may exacerbate deficiency by reducing vitamin D-binding protein (DBP) availability, increasing renal clearance of free 25(OH)D (Anty et al., 2020). Conversely, vitamin D repletion improved albumin synthesis (Δ = +0.5 g/dL, p=0.004), likely via VDR-mediated upregulation of hepatic albumin gene expression (Ding et al., 2013). These bidirectional interactions position vitamin D as both a marker and mediator of hepatic synthetic capacity.

The therapeutic implications of our findings are significant. Cholecalciferol supplementation (2000 IU/day) normalized 25(OH)D levels in 68% of patients and improved MELD scores by 3.6 points (p=0.01), mirroring results from Li et al. (2019), who observed reduced hepatic inflammation in supplemented CLD patients. However, our dosing regimen contrasts with Petta et al. (2014), who used 50,000 IU/week in hepatitis C, highlighting the need for standardized protocols. Notably, the reduction in liver stiffness (Δ = -3.7 kPa, p=0.02) post-supplementation suggests that vitamin D may modulate extracellular matrix remodeling, potentially delaying cirrhosis progression. These benefits, coupled with a favorable safety profile (no hypercalcemia events), advocate for integrating vitamin D screening into routine CLD management.

5. Conclusion

In conclusion, this study establishes vitamin D deficiency as a modifiable risk factor for hepatic decompensation in CLD, with serum 25(OH)D levels serving as a robust correlate of CTP scores and mortality. The improvements in synthetic function, fibrosis, and survival following supplementation underscore the therapeutic potential of vitamin D repletion. These findings advocate for routine screening and targeted supplementation in CLD management, pending validation through RCTs.

6. Limitations

Our study has limitations. First, the observational design precludes causal inferences; unmeasured confounders such as dietary intake or ultraviolet B exposure may influence outcomes. Second, the single-center recruitment limits generalizability to non-tertiary settings. Third, the 6-month supplementation period may underestimate long-term benefits, particularly in slow-progressing etiologies like MASLD. Finally, while transient elastography is a validated non-invasive tool, histological fibrosis staging was available in only 30% of participants, potentially introducing measurement bias.

7. Future Directions

Prospective randomized controlled trials (RCTs) are needed to validate these findings. Priority should be given to optimizing supplementation protocols (e.g., high-dose bolus vs. daily regimens) and evaluating outcomes in non-viral CLD subgroups, such as MASLD, where vitamin D's immunometabolic effects may be particularly relevant (Younossi et al., 2018). Additionally, exploring the integration of vitamin D into prognostic models (e.g., MELD-VitD) could enhance risk stratification and transplant prioritization.

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