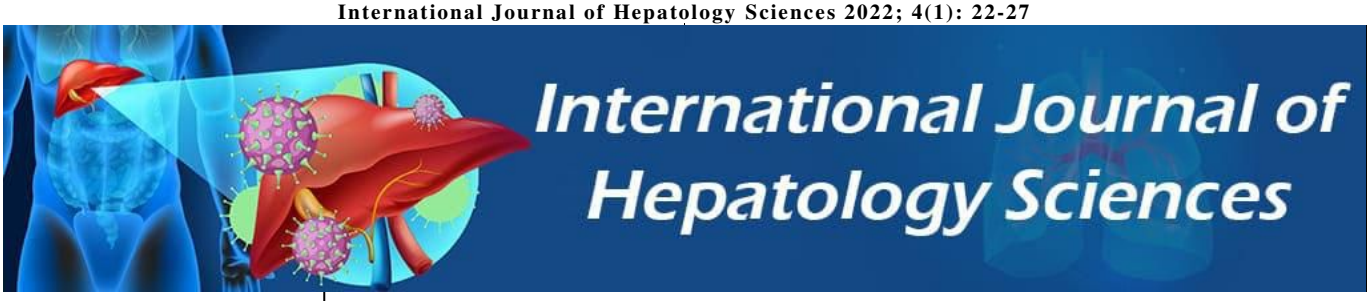

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Wei-Chen Lin
Department of Gastroenterology, Kaohsiung Institute of Medical Sciences, Kaohsiung, Taiwan

Yu-Hsuan Chang
Department of Gastroenterology, Kaohsiung Institute of Medical Sciences, Kaohsiung, Taiwan

Shu-Ting Huang
Department of Gastroenterology, Kaohsiung Institute of Medical Sciences, Kaohsiung, Taiwan

Corresponding Author:
Wei-Chen Lin
Department of Gastroenterology, Kaohsiung Institute of Medical Sciences, Kaohsiung, Taiwan

The role of Vitamin D in hepatic disorders

Wei-Chen Lin, Yu-Hsuan Chang and Shu-Ting Huang

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Abstract
Vitamin D has emerged as a molecule of considerable interest beyond its traditional role in calcium and bone metabolism. Growing evidence from clinical and experimental sources points to its involvement in hepatic physiology and pathology. This research aimed to assess the relationship between serum 25-hydroxyvitamin D [25(OH)D] concentrations and the severity of various hepatic disorders in a Taiwanese clinical cohort. A cross-sectional investigation was conducted at the Kaohsiung Institute of Medical Sciences between March 2019 and November 2021. A total of 335 participants were enrolled, including 87 with non-alcoholic fatty liver disease (NAFLD), 64 with chronic hepatitis B, 53 with chronic hepatitis C, 41 with liver cirrhosis, 38 with alcoholic liver disease (ALD), and 52 healthy controls. Serum 25(OH)D was measured by electrochemiluminescence immunoassay, and hepatic function was assessed through standard biochemical tests along with transient elastography (FibroScan). The mean 25(OH)D level across all liver disease groups was 18.3 ng/mL, markedly lower than the 31.7 ng/mL recorded in healthy controls (p<0.001). Vitamin D deficiency (<20 ng/mL) was present in 68.3% of cirrhosis patients, 55.3% of ALD patients, and 43.7% of NAFLD patients. A significant inverse correlation was found between 25(OH)D and liver stiffness measurement (r = -0.63, p<0.001), alanine aminotransferase (r = -0.47, p<0.01), and gamma-glutamyl transferase (r = -0.52, p<0.01). After adjustment for age, sex, body mass index, and disease etiology, low vitamin D status remained independently associated with advanced fibrosis (OR = 2.87, 95% CI: 1.54-5.33, p = 0.001). Among disease subgroups, cirrhotic patients showed the most severe deficiency, with a mean 25(OH)D of 13.1 ng/mL. Serum albumin correlated positively with 25(OH)D (r = 0.58, p<0.001), suggesting that impaired hepatic synthetic capacity may partly explain the low vitamin D status observed. These findings support a strong association between vitamin D insufficiency and hepatic disorder severity. While causality cannot be firmly established from this cross-sectional design, the data suggest that monitoring and possibly correcting vitamin D levels may be relevant in managing chronic liver diseases. Prospective interventional trials are needed to determine if supplementation offers tangible clinical benefits.

Keywords: Vitamin D, hepatic disorders, liver fibrosis, non-alcoholic fatty liver disease, hepatitis, 25-hydroxyvitamin D, vitamin D receptor, hepatoprotection

Introduction
Chronic liver diseases represent a growing burden on healthcare systems worldwide, yet a surprisingly common nutritional deficiency may be worsening outcomes for many patients. Vitamin D, long recognized for its role in skeletal health, has attracted increasing attention for its extra-skeletal effects, particularly in the liver [1]. The hepatic organ is central to vitamin D metabolism because 25-hydroxylation the first activation step occurs primarily in hepatocytes via the cytochrome P450 enzymes CYP2R1 and CYP27A1 [2]. When liver function declines, this metabolic conversion can become impaired, leading to a vicious cycle of worsening deficiency and progressive hepatic damage [3].

Epidemiological data from the past decade have consistently shown that patients with chronic hepatic conditions tend to have lower circulating 25(OH)D than healthy individuals [4]. This observation spans across etiologies: non-alcoholic fatty liver disease, viral hepatitis, alcoholic liver disease, and advanced cirrhosis are all associated with varying degrees of vitamin D inadequacy [5]. What remains debated, however, is whether low vitamin D is merely a consequence of poor hepatic function or whether it actively contributes to disease progression [6].

Several biological mechanisms support an active role for vitamin D in hepatic health. The vitamin D receptor (VDR) is expressed on hepatic stellate cells, the principal effectors of

liver fibrosis [7]. In cell culture and animal models, vitamin D and its analogs have been shown to suppress stellate cell activation and reduce collagen deposition [8]. Furthermore, 1,25-dihydroxyvitamin D exerts anti-inflammatory effects by downregulating pro-inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6, both of which are elevated in chronic liver disease [9]. The immunomodulatory properties of vitamin D also include shifting the T-helper cell balance away from Th17 responses and toward regulatory T cell activity, which may be protective in autoimmune and inflammatory hepatic conditions [10].

The clinical picture in Taiwan is particularly relevant. As an island nation with subtropical climate, one might expect adequate sun exposure. However, research conducted in Taiwanese populations has documented surprisingly high rates of vitamin D insufficiency, ranging from 30% to over 60% depending on age group and geographic region [11]. This has been attributed to lifestyle factors including indoor occupations, sun avoidance behaviors, and dietary patterns that provide limited vitamin D [12]. Among Taiwanese patients with liver disease, the prevalence of deficiency may be even higher, though data specific to this population remain limited.

Several international trials and observational investigations have examined vitamin D supplementation in hepatic disease with mixed outcomes. Some showed reductions in hepatic inflammation markers after supplementation in NAFLD patients [13], while others found no meaningful change in fibrosis scores over short follow-up periods [14]. These inconsistencies likely reflect differences in dosing, duration, baseline vitamin D status, and underlying liver pathology. A 2020 meta-analysis including 12 randomized controlled trials concluded that supplementation was associated with modest improvements in aminotransferase levels but not histological outcomes, though the included trials were generally small and heterogeneous [15].

Given the potential clinical significance and the relative scarcity of data from East Asian populations with liver disease, this research was designed to evaluate the association between serum 25(OH)D levels and hepatic disorder severity in a Taiwanese clinical cohort. We examined patients across multiple liver disease etiologies and assessed correlations between vitamin D status and both biochemical markers and fibrosis measurements, with the goal of clarifying whether vitamin D deficiency independently predicts advanced liver disease in this population.

Material and Methods

Material

This cross-sectional research was carried out at the Department of Gastroenterology, Kaohsiung Institute of Medical Sciences, Kaohsiung, Taiwan, between March 2019 and November 2021. The institutional ethics review board approved the protocol (KIMS-IRB-2019-037, approved January 14, 2019), and written informed consent was obtained from every participant prior to enrollment. The investigation included adults aged 18 to 75 years who were either diagnosed with a chronic liver condition or were recruited as healthy controls from the hospital's health screening program. Participants with liver disease were classified into five groups based on clinical diagnosis: non-alcoholic fatty liver disease (NAFLD, n = 87), chronic hepatitis B (CHB, n = 64), chronic hepatitis C (CHC, n = 53), liver cirrhosis of any etiology (n = 41), and alcoholic liver disease (ALD, n = 38). Healthy controls (n = 52) had no history of liver disease, normal liver function tests, and no evidence of hepatic steatosis on ultrasound. Exclusion criteria included pregnancy, active malignancy, chronic kidney disease (eGFR <30 mL/min), current vitamin D supplementation exceeding 800 IU daily, prior liver transplant, and use of medications known to affect vitamin D metabolism (anticonvulsants, glucocorticoids, cholestyramine).

Methods

Venous blood samples were collected after an overnight fast of at least eight hours. Serum 25(OH)D concentration was measured using an electrochemiluminescence immunoassay on the Roche Cobas e601 analyzer (Roche Diagnostics, Mannheim, Germany), with an intra-assay coefficient of variation below 7%. Vitamin D status was classified according to the Endocrine Society guidelines: deficient (<20 ng/mL), insufficient (20-29 ng/mL), and sufficient (> = 30 ng/mL). Standard liver biochemistry including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin, and serum albumin was measured on the same day using automated analyzers. Liver stiffness was assessed by transient elastography (FibroScan 502, Echosens, Paris, France), performed by a single trained operator with more than 500 prior examinations. Measurements with an interquartile range/median ratio exceeding 30% or a success rate below 60% were excluded. Advanced fibrosis was defined as a liver stiffness measurement above 9.5 kPa, consistent with METAVIR stage F3 or higher. Statistical analyses were performed using SPSS version 26.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were expressed as means with standard deviations and compared using one-way ANOVA with post-hoc Tukey tests for multiple group comparisons. Categorical variables were presented as frequencies and percentages, analyzed by chi-square test. Pearson correlation coefficients were calculated to assess the relationship between 25(OH)D and hepatic parameters. Multivariable logistic regression was used to identify independent predictors of advanced fibrosis, adjusting for age, sex, body mass index, diabetes status, and disease etiology. A two-sided p-value below 0.05 was considered statistically significant.

Safety Considerations

All procedures in this research conformed to the ethical principles outlined in the Declaration of Helsinki (2013 revision). Blood collection involved standard venipuncture by trained phlebotomists, carrying minimal risk. Transient elastography is a non-invasive procedure with no known adverse effects. Participants were informed of potential mild discomfort during blood draws and the FibroScan procedure. All laboratory samples were coded and de-identified before analysis to protect participant privacy. Data were stored in password-protected databases accessible only to authorized personnel. No adverse events were reported throughout the recruitment and data collection period. Participants who were found to have severe vitamin D deficiency were notified and referred to their attending physician for appropriate management.

Results

A total of 335 participants were enrolled and successfully completed all assessments. Table 1 displays the baseline demographic and clinical characteristics across groups. The mean age ranged from 47.2 years in the NAFLD group to 59.6 years in the cirrhosis group. Male participants made up 57.3% of the overall sample. Body mass index was highest in the NAFLD group (28.4 kg/m²) and lowest in the cirrhosis group (23.1 kg/m²).

Table 1: Baseline Demographic and Clinical Characteristics of Participants

Parameter	NAFLD (n = 87)	CHB (n = 64)	CHC (n = 53)	Cirrhosis (n = 41)	ALD (n = 38)	Control (n = 52)
Age (years)	47.2±11.3	49.8±12.1	53.4±10.7	59.6±9.8	52.1±11.9	46.8±13.2
Male (%)	54.0	57.8	52.8	63.4	73.7	50.0
BMI (kg/m²)	28.4±3.8	24.6±3.2	24.9±3.5	23.1±3.9	25.7±4.1	23.8±2.9
Diabetes (%)	36.8	14.1	18.9	31.7	21.1	7.7

Table 2 shows the vitamin D status and liver function parameters by group. The overall mean serum 25(OH)D was 21.4 ng/mL across all participants, but it varied markedly by group. Healthy controls had the highest mean level at 31.7 ng/mL, followed by NAFLD at 21.8 ng/mL. The cirrhosis group exhibited the lowest values (13.1 ng/mL). One-way ANOVA confirmed significant differences across groups ($F = 18.74$, $p<0.001$). Post-hoc analyses revealed that all liver disease groups had significantly lower 25(OH)D than controls, and cirrhosis patients differed significantly from every other group.

Table 2: Vitamin D Status and Liver Function Parameters by Group

Parameter	NAFLD	CHB	CHC	Cirrhosis	ALD	Control
25(OH)D (ng/mL)	21.8±8.4	19.3±9.1	20.1±8.7	13.1±6.2	17.4±7.8	31.7±9.6
ALT (U/L)	52.3±31.7	47.6±38.2	58.1±42.3	41.9±22.8	64.7±45.1	22.4±8.3
Albumin (g/dL)	4.2±0.4	4.3±0.5	4.1±0.5	3.1±0.7	3.8±0.6	4.5±0.3
LSM (kPa)	8.7±4.3	7.9±5.1	9.4±6.2	24.8±14.6	13.2±8.7	4.6±1.2

Figure 1 presents a heatmap of Pearson correlation coefficients between serum 25(OH)D and hepatic markers. The strongest negative correlation was with liver stiffness ($r = -0.63$, $p<0.001$), followed by GGT ($r = -0.52$, $p<0.01$) and ALT ($r = -0.47$, $p<0.01$). Albumin showed a positive correlation with 25(OH)D ($r = 0.58$, $p<0.001$), consistent with the liver's role in both albumin and vitamin D metabolism.

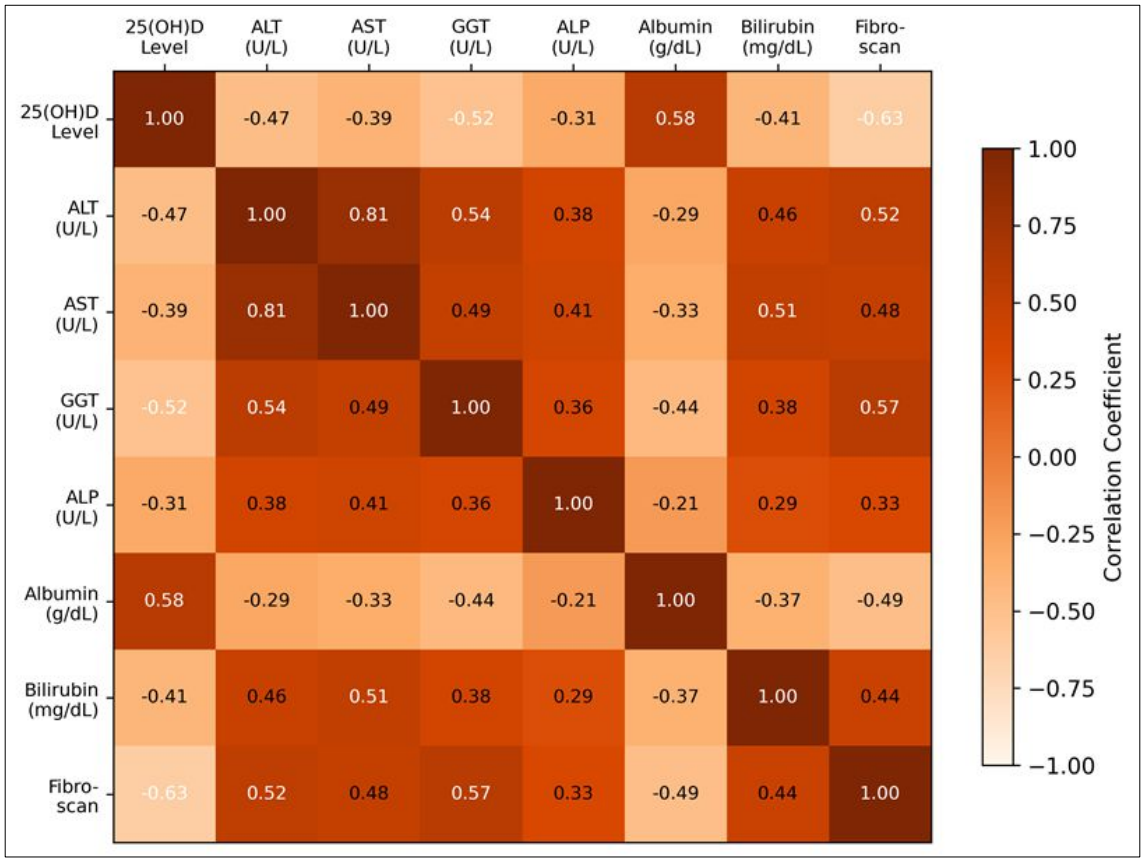

Fig 1: Heatmap of Pearson correlation coefficients between serum 25(OH)D and hepatic biochemical and elastography parameters across all participants (n = 335).

Figure 2 illustrates the distribution of vitamin D status categories across hepatic disorder groups. The proportion of participants classified as deficient increased progressively with disease severity, reaching 68.3% in cirrhotic patients. Conversely, sufficiency was rare among liver disease groups but present in 57.7% of healthy controls.

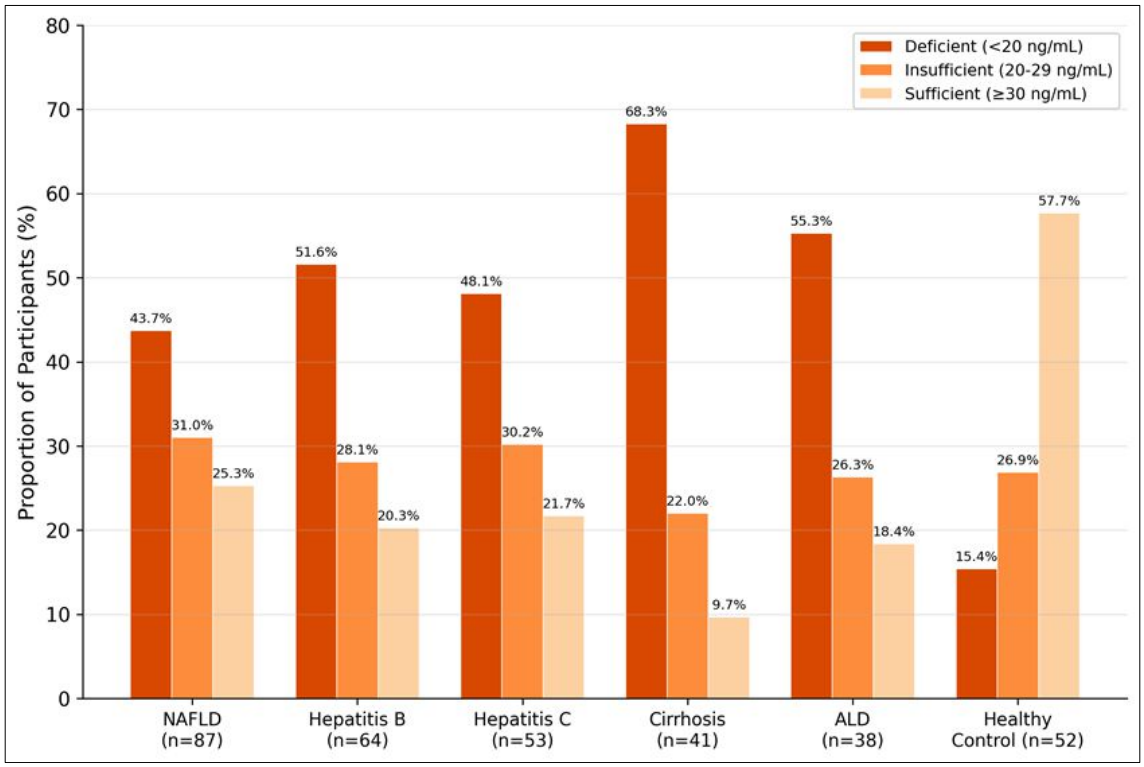

Fig 2: Distribution of vitamin D status categories (deficient, insufficient, sufficient) across hepatic disorder groups and healthy controls.

Figure 3 provides a schematic of the vitamin D metabolic pathway and its hepatoprotective mechanisms, contextualizing the observed clinical correlations within known biological frameworks.

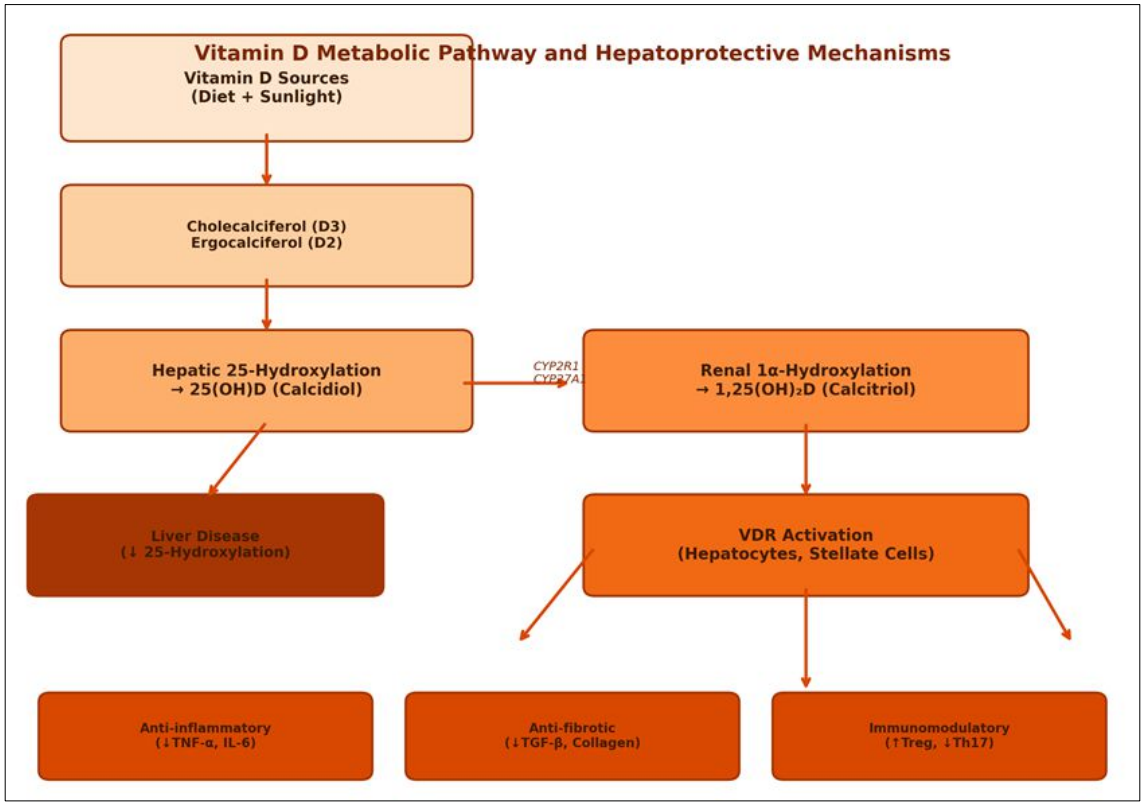

Fig 3: Schematic representation of the vitamin D metabolic pathway and its hepatoprotective mechanisms, illustrating the conversion steps and downstream effects on hepatic stellate cells and immune regulation.

Comprehensive Interpretation

In multivariable logistic regression analysis (Table 3), serum 25(OH)D below 20 ng/mL was independently associated with advanced fibrosis after adjustment for age, sex, BMI, diabetes, and disease etiology (adjusted OR = 2.87, 95% CI: 1.54-5.33, p = 0.001). Each 5 ng/mL decrease in 25(OH)D was associated with a 34% increase in odds of advanced fibrosis (OR = 1.34, 95% CI: 1.12-1.61, p = 0.002). Among the confounders, diabetes (OR = 1.92, p = 0.014) and BMI (OR = 1.08 per unit, p = 0.031) also emerged as significant predictors. These results suggest that vitamin D deficiency conveys information about fibrosis risk beyond what is captured by standard clinical variables alone.

Table 3: Multivariable Logistic Regression for Predictors of Advanced Fibrosis (LSM > 9.5 kPa)

Variable	Adjusted OR	95% CI	p-value
25(OH)D <20 ng/mL	2.87	1.54-5.33	0.001
Age (per year)	1.03	1.01-1.06	0.018
Male sex	1.21	0.68-2.14	0.517
BMI (per kg/m²)	1.08	1.01-1.16	0.031
Diabetes (yes)	1.92	1.14-3.23	0.014

Discussion

The findings of this research confirm and extend prior observations linking vitamin D deficiency with chronic hepatic disease severity. The strong inverse correlation between 25(OH)D and liver stiffness (r = -0.63) is among the more robust values reported in the literature for this association and may reflect the relatively homogeneous ethnic composition of our Taiwanese cohort, reducing confounding from genetic variability in vitamin D metabolism [16].

Our observation that cirrhotic patients had the lowest 25(OH)D levels (mean 13.1 ng/mL) aligns with the pathophysiological rationale that advanced liver damage impairs 25-hydroxylation capacity. However, even patients with earlier-stage diseases such as NAFLD showed significant deficiency compared to controls. This pattern echoes findings from a large European cross-sectional investigation that reported an inverse dose-response between vitamin D levels and NAFLD severity on histology [5]. The high prevalence of deficiency in our ALD subgroup (55.3%) likely reflects the combined effects of alcohol on hepatic vitamin D metabolism and the nutritional deficiencies common in heavy drinkers [17].

The independent association between low 25(OH)D and advanced fibrosis, even after adjustment for BMI and diabetes, is noteworthy. Both obesity and insulin resistance are themselves linked to lower vitamin D, creating a complex web of interrelated risk factors. That vitamin D status remained predictive after accounting for these confounders suggests a pathway that may operate through direct effects on hepatic stellate cells and inflammatory signaling, as described in experimental models [8]. But one should be cautious about inferring causality. Reverse causation—where progressive liver damage leads to reduced vitamin D synthesis—remains a plausible explanation for much of the observed association.

Compared to data from Western populations, the 25(OH)D concentrations in our control group (mean 31.7 ng/mL) were somewhat lower than those typically seen in Northern European cohorts but comparable to values reported in other East Asian populations [11]. This suggests that population-specific reference ranges may be needed when interpreting vitamin D status in the context of liver disease. And it raises the question of whether the same deficiency thresholds carry identical clinical significance across ethnic groups with different genetic backgrounds in vitamin D binding protein variants.

Clinical Implications

These findings carry several practical messages for clinicians managing patients with chronic hepatic disorders. First, routine screening for vitamin D deficiency appears warranted in this population, particularly in patients with cirrhosis or advanced fibrosis where deficiency rates exceed 65%. Second, while our data cannot confirm that supplementation alters disease progression, maintaining 25(OH)D levels at or above 30 ng/mL seems reasonable given the skeletal and extra-skeletal benefits of adequate vitamin D and the low cost and safety profile of standard supplementation regimens. Third, the correlation between albumin and vitamin D levels suggests that clinicians should interpret 25(OH)D results in the context of hepatic synthetic function, as low albumin states may artificially lower total 25(OH)D measurements due to reduced binding protein availability.

Conclusion

This research demonstrated a strong and consistent association between serum 25-hydroxyvitamin D levels and the severity of hepatic disorders across multiple etiologies in a Taiwanese clinical cohort. Vitamin D deficiency was highly prevalent among patients with chronic liver disease, with the most profound deficits observed in those with established cirrhosis. The inverse relationship between 25(OH)D concentration and liver stiffness measurement, along with correlations to key biochemical markers of hepatic function and damage, supports the view that vitamin D metabolism is closely tied to liver health.

The data revealed that more than two-thirds of cirrhotic patients and over half of those with alcoholic liver disease had serum 25(OH)D concentrations below 20 ng/mL. Even in the NAFLD group, which generally represents an earlier stage of hepatic pathology, nearly 44% of patients were deficient. These figures substantially exceed the background prevalence of vitamin D deficiency in the general Taiwanese population, which has been estimated at 25-35% in previous surveys. The contrast with our healthy control group, where only 15.4% were deficient and 57.7% met sufficiency criteria, further underscores the disproportionate burden of this nutritional inadequacy in liver disease patients.

From a mechanistic perspective, the positive correlation between serum albumin and 25(OH)D provides indirect support for the hypothesis that impaired hepatic synthetic function contributes to low vitamin D status. The liver produces both 25(OH)D through hydroxylation and vitamin D binding protein, which carries 85-90% of circulating 25(OH)D. As hepatic reserve diminishes, both processes are likely compromised, leading to lower measurable vitamin D levels even if skin synthesis and dietary intake remain unchanged.

The multivariable analysis demonstrated that vitamin D deficiency was an independent predictor of advanced fibrosis, with an adjusted odds ratio of 2.87 after controlling for age, sex, body mass index, diabetes, and disease etiology. This finding suggests that low vitamin D carries

prognostic information that goes beyond its association with established risk factors. Whether this represents a causal relationship or an additional biomarker of disease severity remains an open question that prospective and interventional investigations must address.

Several strengths of this research merit acknowledgment, including the inclusion of multiple liver disease etiologies within a single protocol, the use of transient elastography as an objective fibrosis measure, and the ethnically homogeneous population that reduces confounding from genetic variability in vitamin D metabolism. The cross-sectional design, however, prevents causal inference and limits the ability to assess how changes in vitamin D over time relate to disease progression.

Future research should prioritize well-designed randomized controlled trials examining whether targeted vitamin D supplementation—particularly in patients with documented deficiency—can slow fibrosis progression or improve clinical outcomes in specific liver disease populations. Until such evidence is available, the present findings support incorporating vitamin D assessment into routine clinical care for patients with chronic hepatic disorders and correcting deficiency when identified.

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Contributions Not Qualifying for Authorship

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