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Original Article

Vitamin D Deficiency and Chronic Liver Disease: Investigating Predictive Factors and Their Implications for Patient Care in Pakistan

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Abstract

Background: Chronic liver disease (CLD) and its end-stage manifestation, cirrhosis, present significant global health challenges, contributing to substantial morbidity and mortality. Despite its impact on various organ systems, the musculoskeletal effects of CLD, particularly vitamin D deficiency remain underexplored. This study aimed to identify significant predictors of vitamin D deficiency among CLD patients.

Methods: Overall, 177 CLD patients of either gender, aged 18 yr and above were included using the non-probability consecutive sampling technique. This cross-sectional study was conducted at the medical units of Isra University Hospital, Hyderabad, from Jan to Jun 2023. Various markers of hepatic function including bilirubin, albumin, and International normalised ratio (INR), were analyzed, along with a complete blood count and each patient was assigned a Child-Turcotte-Pugh (CTP) score. The relationship of vitamin D with different variables was assessed through Chi-Square tests. Pearson correlation and regression analyses were carried out to identify predictors of vitamin D deficiency.

Results: Mean age of patients was 51.76±5.77 yr and the majority were male (68.4%). Vitamin D deficiency was present in 28.24%, particularly among those with cirrhosis. Vitamin D levels correlated negatively with disease severity, as indicated by CTP (P<0.05) and Model for End-Stage Liver Disease (MELD) (P<0.05) scores, and positively with albumin levels (P<0.05). Increasing age, male gender, and higher CTP and MELD scores were significant predictors (P<0.05) of vitamin D deficiency.

Conclusion: Vitamin D levels correlate with hepatic dysfunction and are negatively associated with disease progression. Significant predictors of vitamin D deficiency identified include increasing age, male gender, and higher MELD and CTP Score.

Keywords: Chronic liver disease; Liver cirrhosis; Vitamin D; Vitamin D deficiency

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Introduction

Chronic liver disease (CLD) is marked by a prolonged decline in liver function, affecting its ability to synthesize clotting factors, detoxify metabolic waste, and secrete bile (1). CLD is an ongoing cycle of inflammation, destruction, and regeneration of hepatic parenchyma, ultimately leading to fibrosis and cirrhosis (2). Liver cirrhosis, the end stage of CLD, disrupts liver structure, leads to nodular development, neo-angiogenesis, vascular reorganization, and extracellular matrix deposition (3). Causing an estimated 2 million deaths each year, CLD, along with cirrhosis, is a significant public health challenge worldwide, contributing to an elevated burden of disability and increased utilization of healthcare services (4). Although various factors can contribute to the development of CLD, including chronic hepatitis B virus (HBV) infection, nonalcoholic steatohepatitis (NASH), consumption of alcohol, cholestatic disorders, chronic vascular obstruction, and autoimmune diseases, the preeminent etiological factor responsible is the hepatitis C virus (5, 6).

The primary complication of CLD that frequently leads to hospitalization is ascites, followed by hepatic encephalopathy and infection (7). Other complications include anemia, portal hypertension, gastrointestinal bleeding, hepatorenal syndrome, esophageal variceal bleeding, portal vein thrombosis, etc (8). Another aspect of liver cirrhosis that is not extensively studied involves its effects on the musculoskeletal system.

CLD initiates a complex interplay involving parathyroid hormone, serum calcium, phosphate, and vitamin D levels, which in turn affects the musculoskeletal system (9). These disturbances can lead to bone mineral density loss, impaired bone formation, and an increased risk of fractures, leading to a spectrum of metabolic bone disorders collectively referred to as Hepatic Osteodystrophy (HOD) (10). HOD affects over 844 million individuals globally, and nearly 75% of those with HOD experience osteopenia or osteoporosis, significantly contributing to the morbidity of cirrhotic patients (10, 11). One of the most critical factors attributed to the development of HOD is the deficiency of vitamin D (12).

Vitamin D, an essential lipid-soluble vitamin, is also called a regulator of mineral homeostasis and bone metabolism (13). Besides playing an important role as a micronutrient in the body, it also acts as a vital hormone involved in an intricate and multifaceted system affecting skeletal muscle integrity, immunomodulation, cellular proliferation, and differentiation (14). Vitamin D is essential for calcium metabolism and bone health, and sufficient levels also lower the risk of chronic diseases like diabetes, infections, and cancers such as breast, prostate, and colon. This protective effect is attributed to widespread vitamin D receptor expression on cell surfaces, including hepatocytes, macrophages, and immune B and T cells (15, 16).

Patients with CLD commonly experience a high prevalence of vitamin D deficiency, with more than 90% of patients reporting some degree of insufficiency (17). It even affects patients suffering from mild liver disease; however, patients suffering from liver cirrhosis are more commonly susceptible to experiencing severe deficiency (17, 18). Potential mechanisms responsible for this are 1) Cholestasis, caused by CLD, which leads to impaired absorption of fats and fat-soluble vitamins; 2) Dietary deficiency of vitamin D secondary to anorexia of chronic disease; 3) CLD-induced morbidity and decreased mobility, resulting in restricted exposure to sunlight; 4) Reduced hepatic 25-hydroxylation of cholecalciferol in CLD (19).

Vitamin D deficiency is an often-overlooked aspect of CLD, yet it significantly impacts the morbidity of patients. The main objective of this study was to investigate the significant predictors of vitamin D deficiency among CLD patients. Furthermore, we also aimed to explore the corre-

lation of Vitamin D deficiency with the Child-Pugh class classification system for liver cirrhosis.

Material and Methods

Study setting and design

This cross-sectional study was conducted at the medical units of Isra University Hospital, Hyderabad, from Jan to June 2023.

Ethical consideration

The study received approval from the Isra University Ethical Review Board (ERB letter no: IU/RR-10-IRC-22/N/2022/514) and followed the principles outlined for medical research involving human subjects as stated in the Declaration of Helsinki (20). The study participants were counselled regarding the objectives of the study along with the potential advantages associated with their participation, after which informed written consent was obtained, and their anonymity was guaranteed.

Study population

Participants were selected through a non-probability consecutive sampling technique. Patients were classified as having CLD if they exhibited any of the following characteristics: abnormal biochemical profiles (e.g., disrupted liver function tests persisting for more than 3 months), ultrasonographic indications (such as surface irregularities, coarse hepatic texture, lobar or segmental hypertrophy, or atrophy), evidence of chronic alterations of the hepatic parenchyma observed through liver biopsy, or documented medical history indicating CLD. A sample size of 177 was estimated using a population proportion sample-size-calculator with a 92% vitamin D deficiency prevalence among CLD patients (21), keeping the confidence interval at 95% and a margin of error of 4%. The inclusion criteria were CLD patients of either gender, aged 18 yr and above. Whereas patients taking medications that affect levels of Vitamin D (calcium or vitamin D supplements, corticosteroids, antiepileptics, and bisphosphonates) and those with conditions that could potentially disturb vitamin D metabolism, such as renal failure, malabsorption disorders, or tuberculosis, were excluded.

Clinical Evaluation

A comprehensive evaluation of the patient's clinical history and thorough physical examination were conducted. Blood samples were collected for hematological and biochemical workup, which included measurement of International Normalized Ratio (INR) using a Sysmex CA-1500 analyzer (Sysmex Corporation, Kobe, Japan), serum levels of bilirubin analyzed on a Beckman Coulter AU5800 chemistry analyzer (Beckman Coulter, Brea, USA), and 25-hydroxyvitamin D (Catalogue no: MBS4500005, MyBioSource, San Diego, USA) measured with an ELISA kit. Complete blood count, including hemoglobin level, total leukocyte count, and platelet count, was conducted using a Sysmex XN-1000 hematology analyzer (Sysmex Corporation, Kobe, Japan). Ascites was graded as mild, moderate, and severe based on whether it was visible only on ultrasound, caused moderate symmetrical abdominal distension, or marked abdominal distension, respectively (22). This grading was independently assessed by two different radiologists to ensure accuracy and consistency. West Haven criteria (WHC) was used to grade hepatic encephalopathy from grade 0 to IV (23). During endoscopy, esophageal varices were classified into grades I to IV using Paquet's grading method (24). The Child-Turcotte-Pugh (CTP) classification and Model for End-Stage Liver Disease (MELD) score were assessed for every individual in the study (25). Based on vitamin D levels, patients were divided into sufficient (>31 ng/mL), insufficient (21-30 ng/mL), and deficient (<20 ng/mL) groups (26).

Statistical Analysis

Statistical Package for Social Sciences (SPSS) ver. 22.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism version 8 (GraphPad Software Inc.; San Diego, CA, USA) were used for Statistical analysis. Mean ± Standard deviation (SD) was used to represent continuous variables, while fre-

quencies and percentages were used to present categorical variables. The comparison of continuous and categorical variables was performed using One-way ANOVA and Chi-Square tests, respectively. The correlation between multiple variables was assessed using the Pearson correlation matrix, while the relationship between vitamin D and various variables was assessed using linear regression analysis. Additionally, univariate and multinomial regression analyses were performed to predict vitamin D deficiency among patients. Level of statistical significance was established at *P*-value of ≤ 0.05.

Results

Overall, 177 eligible patients (mean age 51.76 ± 5.77 yr; age range 39-63 yr) with CLD were included in the study. The most common etiological factor was HCV followed by alcoholic. The mean vitamin D level was 26.63±6.39 ng/mL, and most of the patients had sufficient levels (89 patients; 50.28%), followed by deficient (50 patients; 28.24%) and insufficient levels (38 patients; 21.46%), respectively. Among those suffering from cirrhosis, most had deficient (50 patients; 60.24%) and insufficient (31 patients; 37.34%) vitamin D levels, respectively. Based on the CTP score, most of the patients were in class A (76 patients; 42.93%), followed by class C (69 patients; 38.98%) and class B (32 patients; 18.07%), respectively (Table 1).

Table 1: Overview of Baseline Characteristics (n=177)

Study variables	n (%)
Cirrhosis	
• Present	83 (46.89)
• Absent	94 (53.10)
Sex	
• Male	121 (68.4)
• Female	56 (31.6)
Etiology	
• HCV	113 (63.84)
• Alcoholic	41 (23.16)
• AIH	13 (7.34)
• PBC	20 (11.29)
• NAFLD	7 (3.95)
Ascites (%)	
• None	110 (62.0)
• Moderate or under tension	40 (22.6)
• Portal Vein Thrombosis	22 (12.6)
• Hepatocellular Carcinoma	05 (2.8)
Varices	
• No Varices	61 (34.46)
• Grade I	47 (26.55)
• Grade II	39 (22.03)
• Grade III	30 (16.94)

AIH-autoimmune hepatitis; HCV-hepatitis C virus;
PBC-primary biliary cirrhosis; NAFLD-nonalcoholic fatty liver disease

The association between vitamin D levels and the CTP class is illustrated in contingency Table 2. A statistically significant relationship (P<0.05) was identified between CTP classification and vitamin D levels. The majority of patients in CTP class C exhibited low levels of vitamin D compared to those in CTP class A and B (Table 2).

Table 2: Relationship between Child-Turcotte-Pugh class and Vitamin D level

	Child-Pugh class			Total	*P*-value
	A	B	C		
Vitamin D Level	n (%)	n (%)	n (%)	n (%)	
Sufficient	74 (97.36)	14 (43.75)	1 (1.44)	89 (50.28)	0.000*
Insufficient	1 (1.31)	16 (50)	21 (30.43)	38 (21.46)	
Deficient	1 (1.31)	2 (6.25)	47 (68.11)	50 (28.24)	
Total n (%)	76 (42.93)	32 (18.07)	69 (38.98)	177	

*Chi-square (statistically significant)

Similarly, patients having deficient vitamin D levels exhibited lower hemoglobin levels and higher levels of serum bilirubin, serum albumin, MELD score, and CTP score, as compared with patients having insufficient or sufficient levels of vitamin D. The difference among the groups was statistically significant (P< 0.05) (Table 3).

Table 3: Distribution of variables based on vitamin D levels (n=177)

Study variables	Sufficient	Insufficient	Deficient	P-value
	Mean ± SD			
Age (yr)	47.29±4.03	54.44±2.64	57.68±2.76	0.000*
Hemoglobin (g/dL)	13.23±1.23	10.93±1.05	9.07±1.02	0.000*
WCC (x10^3 cells/L)	6.1±3.2	6.3±3.1	6.5±3.5	0.781
INR (seconds)	1.17±0.23	1.70±0.28	2.21±0.24	0.000*
Platelets (x10^3 cells/L)	137.1±75.5	118.7±72.7	94.3±69.4	0.005*
Serum Bilirubin (µmol/L)	29.35±4.23	46.30±14.84	71.08±20.90	0.000*
ALT (U/L)	52.7±37.1	55.8±36.5	65.4±32.3	0.131
Serum Albumin (g/L)	40.40±7.22	31.68±3.46	25.89±4.64	0.00*
MELD Score	15.3±5.4	19.1±6.3	23.2±6.8	0.000*
CTP Score	5.65±0.90	9.26±1.51	13.10±1.87	0.000*

* ANOVA (Statistically significant)

Figure 1 is depicting the correlation matrix of vitamin D with different study variables. A statistically signficant (P<0.001) negative correlation between vitamin D levels and patient age, CTP score, serum bilirubin and INR was observed. Conversely, a statistically significant (P<0.001) positive correlation was noted between vitamin D and hemoglobin levels as well as serum albumin (Fig. 1).

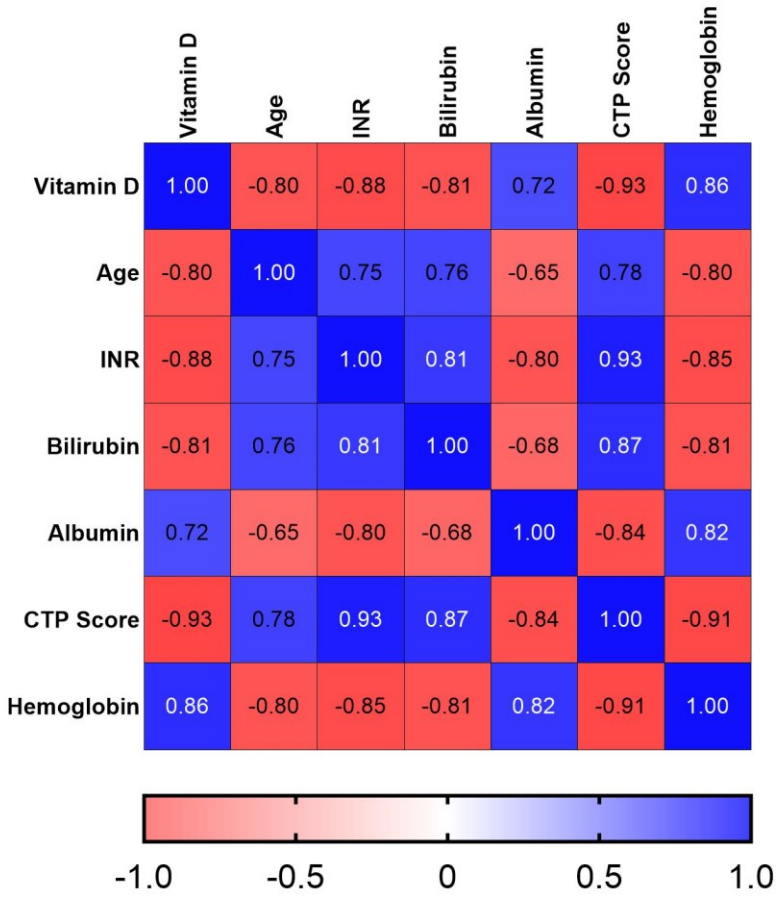

Fig. 1: Multivariate correlation matrix heatmap

The linear regression analysis of vitamin D with age (R2=0.60, *P*<0.001); CTP score (R2=0.82, *P*<0.001); Bilirubin (R2=0.64, *P*<0.001); Albumin (R2=0.49, *P*<0.001); Hemoglobin (R2=0.93, *P*<0.001); INR (R2=0.96, *P*<0.001) is showed in Fig. 2.

According to the model-fitting data, which included a chi-square test value of 90.3 and a p-value of 0.00, the model was statistically fit. The model correctly identified 93.5% of instances and covered 54% to 63% of the variance in the variables (Cox and Snell pseudo-R2 and Nagelkerke pseudo-R2, respectively). Age, MELD score, and the CTP score were discovered to be quantitative factors that predicted vitamin D insufficiency. The qualitative factors of the male sex and CTP class were revealed to be predictive of low vitamin D levels. In our investigation, there was no evidence that the etiology of CLD predicted low vitamin D levels (Table 4).

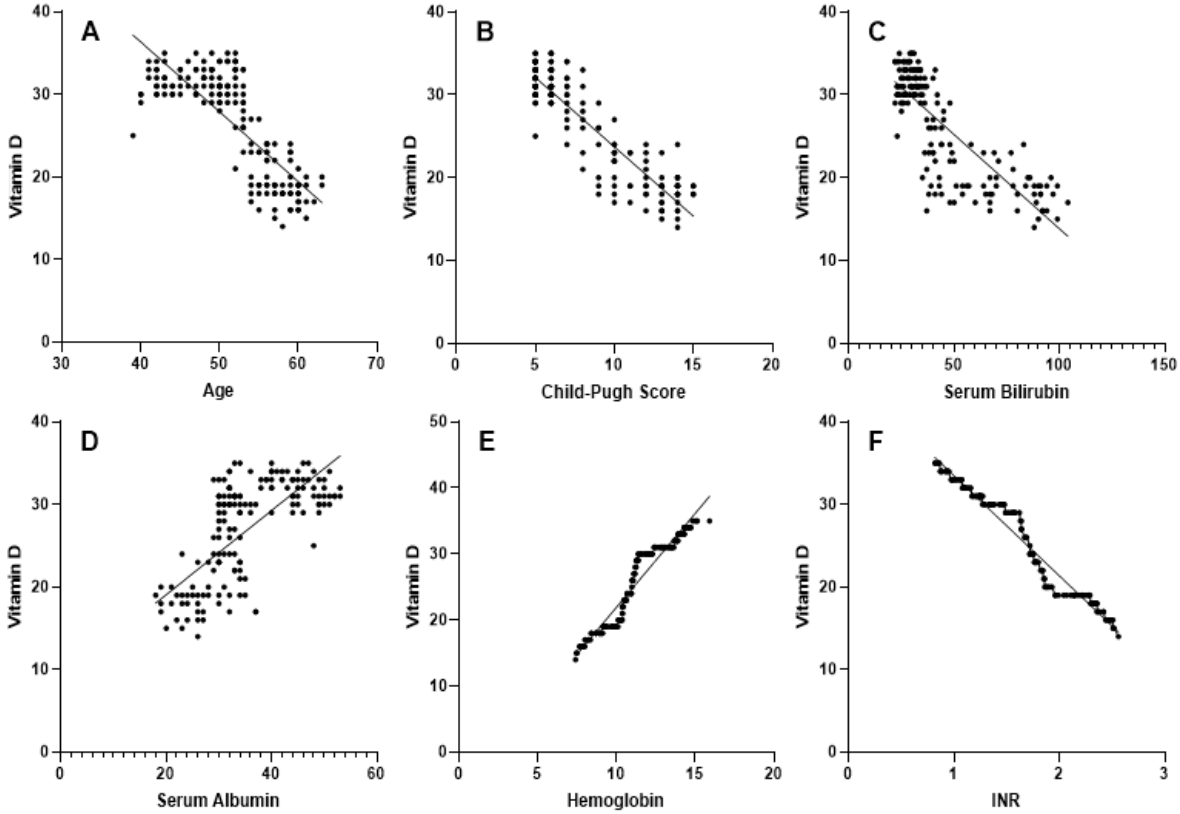

Fig. 2: Linear regression analysis of vitamin D and different study variables

Table 4: Predicting factors of vitamin D using univariate and multinomial regression analysis

Study variable	Univariate		Multinomial		
	OR (95% CI)	*P*-value	χ2	OR (95% CI)	*P*-value
Sex (Male vs Female)	1.8 (1.6-1.8)	0.00*	47.1	-	0.00*
Age	3.6 (3.6-4.2)	0.00*	69.8	1.4(1.2-1.4)	0.00*
Etiology	1.5 (0.6-2.3)	0.52	0.74	-	0.94
Score MELD	2.7 (2.5-3.1)	0.00*	26.9	1.3 (1.1-1.4)	0.00*
Score CTP	2.9 (2.4-3.3)	0.00*	33.0	2.2 (1.46-2.9)	0.00*
Class CTP	1.3 (1.1-1.5)	0.00*	42.8	0.1 (0.0-0.2)	0.00*

*Regression analysis (Statistically significant)

Discussion

With more than 90% of patients reporting some degree of insufficiency, vitamin D deficiency is pervasive in CLD, serving as the leading cause of HOD (12, 17). This study sought to evaluate the prevalence of vitamin D deficiency among CLD patients and to gain a better understanding of its potential association with various clinical parameters.

In this study, the mean vitamin D levels among patients with CLD were recorded at 26.63±6.39 ng/mL, with 28.24% of CLD patients exhibiting deficient levels of vitamin D. Notably, more than

90% of cirrhotic patients displayed either deficient or insufficient levels of vitamin D. Consistent with our findings, Zhao et al (27) and Kumar et al (28) also reported significantly deficient vitamin D levels in cirrhotic patients. Similarly, studies conducted in Spain and Pakistan revealed subnormal vitamin D levels in 87% and 88% of cirrhotic patients, respectively (26, 29). The multifaceted causes of decreased vitamin D levels in cirrhosis are well documented, with hepatic vitamin D hydroxylation inhibition being primarily implicated in this phenomenon (19, 30). At a medical facility in Riyadh, Saudi Arabia, also observed significantly lower vitamin D levels in both CLD and cirrhotic patients compared to controls (31). These findings corroborate our study, suggesting that vitamin D levels tend to be generally low in CLD patients, particularly among those with cirrhosis.

In our present study, vitamin D levels exhibited a negative correlation with both CTP and MELD scores, indicating that as disease severity increases, vitamin D levels tend to decrease. This observation is in line with the results reported earlier (17, 26, 32), all of whom found a similar decline in vitamin D levels as liver disease progressed. Vitamin D levels positively correlated with albumin levels; however, a negative correlation was observed with age and bilirubin levels in the current study. This observation also aligns with the findings of Jamil et al (26) and Khan et al (17). By affecting the gene expression and proliferation of fibroblasts, vitamin D reduces the fibroblast activity of hepatic stellate cells, inflammation, and oxidative stress (32). The deficiency of vitamin D, therefore, favors the progression of fibrosis and disrupts clinical parameters.

Of particular importance in the current study is the identification of increasing age, gender, MELD and CTP scores, and CTP class as significant predictors of vitamin D deficiency. These findings align with those reported by Jamil et al (26). However, Jamil et al documented a greater incidence of vitamin D deficiency among females, which differs from the observations in our study. This difference can be attributed to the demographic composition of the two studies; notably, the majority of participants in their study were females (92%), while the current study predominantly included male participants (68.4%).

Vitamin D deficiency is common in CLD and is linked not only with musculoskeletal manifestations like HOD but also with a multitude of systemic complications, including compromised immunity, increased risk of infections, and progression of liver fibrosis, particularly in cirrhotic patients (31, 32). Since vitamin D levels are directly linked with markers of hepatic dysfunction, recent studies have also highlighted the importance of vitamin D levels as a potential marker to predict histological alterations in hepatic architecture as well as a valuable predictor of severity and mortality in liver disease (19).

However, despite its strengths, the current study has certain limitations. First, this was a single-center study, which may have limited the demographic diversity and generalizability of data. Second, this study lacked a control group that could have aided in assessing the levels of vitamin D and its relation with markers of hepatic function in healthy individuals. Lastly, the effects of vitamin D supplementation on CLD patients were not observed in the current study. Therefore, further research, including intervention studies or randomized clinical trials, is recommended to elucidate not only the potential benefits but also the optimal dosage of vitamin D supplementation in CLD patients and its impact on markers of hepatic dysfunction.

Conclusion

Vitamin d levels correlate with hepatic dysfunction and are negatively associated with disease progression. Significant predictors of vitamin d deficiency identified include increasing age, male gender, and higher meld and CTP scores. These findings underline the significance of monitoring vitamin d levels in clinical practice and may warrant the use of intervention strategies for at-risk populations

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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