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Article

Potential benefits of vitamin d intake for improving outcomes in critical care patients receiving renal replacement therapy: A retrospective study based on the MIMIC-IV database

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Abstract: Background: Vitamin D is essential for numerous physiological functions. Earlier research has unraveled a significant correlation between vitamin D insufficiency and poor outcomes within intensive care unit (ICU) patients. Patients receiving renal replacement therapy (RRT) often experience vitamin D deficiency or insufficiency. Beyond metabolic regulation, vitamin D influences cellular biomechanics, enhancing resilience to mechanical stress and supporting tissue integrity, which are critical for ICU patients undergoing RRT. This research seeks to examine the influence of vitamin D intake on outcomes in ICU patients receiving RRT. **Methods:** This study examined data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. It included all adult patients undergoing RRT. The participants were grouped into two categories: administrated vitamin D throughout their ICU admission (vitamin D group) and did not administer (non-vitamin D group). In-hospital mortality (IHM) was the primary outcome measured. Kaplan-Meier (KM) method Cox regression models, and subgroup analyses were leveraged to evaluate the correlation between vitamin D intake and IHM. To strengthen the reliability of the conclusions, propensity score matching (PSM) was implemented. **Results:** A total of 1270 patients on RRT participated in this research, comprising 338 and 932 patients in the vitamin D and non-vitamin D groups, respectively. The KM survival curves indicated substantial differences in survival probabilities between the two categories. Following adjustments for possible confounding factors by Cox regression analysis, vitamin D intake was markedly related to a reduced likelihood of IHM (HR: 0.35; 95% [CI]: 0.19–0.63; $p < 0.001$). This association remained robust following propensity score matching (PSM). Further subgroup analysis exposed that vitamin D intake reduced the probability of IHM in liver disease patients. **Conclusion:** Vitamin D intake is independently correlated with a reduced likelihood of IHM in ICU patients undergoing RRT. Further interventional studies are warranted to validate the possible advantages of vitamin D intake in improving the health of RRT patients. This study provides robust evidence supporting the therapeutic potential of vitamin D supplementation. These findings highlight the need for personalized supplementation strategies to optimize outcomes in this vulnerable population.

Keywords: intensive care unit; renal replacement therapy; vitamin D

1. Introduction

Vitamin D is a fat-soluble nutrient, whose physiological functions, particularly in calcium and phosphorus metabolism, are well-established. Increasing evidence further suggests that vitamin D helps regulate immune function, inflammation, glucose metabolism, cell proliferation, and apoptosis [1,2]. The extent of vitamin D inadequacy among ICU patients can range from 70% to 95% [3–5]. Numerous research has indicated that Vitamin D inadequacy is strongly related to an elevated

probability of mortality, prolonged hospital stays, and higher rates of complications such as infections like sepsis in ICU patients [6–8].

RRT is a treatment used to help patients eliminate toxins from the blood and promote kidney function recovery. It is routinely employed in clinical care and is an essential tool for saving the lives of critically ill patients [9]. Recent studies have indicated that up to 8%–10% of ICU patients undergo RRT [10]. Improving outcomes in these patients is of significant clinical importance. ICU patients undergoing RRT demonstrate a greater frequency of vitamin D insufficiency in contrast to other patients [5], suggesting that this group may gain more benefits from vitamin D intake. However, there is currently no literature reporting the effect of vitamin D intake on ICU patients receiving RRT. Thus, we conducted a large-scale retrospective analysis to ascertain the possible advantages of vitamin D intake in ICU patients receiving RRT.

2. Methods

2.1. Data source

We engaged in a single-center retrospective cohort study, analyzing data from the MIMIC-IV database, developed and maintained by the MIT Computational Physiology Lab. This extensive publicly accessible database includes detailed and anonymized clinical data from more than 380,000 patients at the Beth Israel Deaconess Medical Center, based in Boston, Massachusetts, covering the years 2008 to 2019. Given that the data is publicly available, informed consent was waived. After completing the collaborative institution's online training program, the principal investigators were granted access to the database (Record ID: 62366615). This research aligned with the criteria outlined in the Declaration of Helsinki. However, as a retrospective study relying on secondary data, our analysis faced inherent limitations. Potential unmeasured confounders, such as dietary intake, sunlight exposure, and specific comorbid conditions, may have influenced the outcomes but were not captured in the dataset. These limitations highlight the need for prospective studies to address these gaps and validate our findings.

2.2. Study population

We retrospectively retrieved data on patients who underwent RRT from the database. Exclusion criteria were as follows: (1) age <18 years; (2) For patients with a history of multiple hospitalizations, only data from their first admission were analyzed. Patients were split into vitamin and non-vitamin D groups based on whether they administrated vitamin D (either intravenous or oral).

2.3. Data extraction and outcome measures

A range of variables, including demographic characteristics, were extracted from the MIMIC-IV 2.2 database for analysis, such as age, sex, and race. We collected clinical data at admission, including vital signs such as heart rate (HR), oxygen saturation (SpO2), temperature, mean arterial pressure (MAP), and respiratory rate (RR). Laboratory tests measured parameters like hemoglobin, aspartate aminotransferase (AST), WBC count, alanine aminotransferase (ALT), total bilirubin

(TBIL), blood urea nitrogen (BUN), platelets, albumin, sodium, 25-hydroxyvitamin D [25(OH)D], B-type natriuretic peptide (BNP), phosphorus, potassium, parathyroid hormone (PTH), prothrombin time (PT), creatinine, blood glucose, calcium, international normalized ratio (INR), C-reactive protein (CRP), lactate, and pH. Additionally, we recorded comorbidities, including cerebrovascular disease, diabetes, kidney disease, myocardial infarction, heart failure, cancer, peripheral vascular disease, dementia, chronic lung disease, rheumatologic conditions, paralysis, peptic ulcers, liver disease, metastatic tumors, and HIV/AIDS. To determine the severity of the condition and consciousness level, we collected Sequential Organ Failure Assessment (SOFA) scores, Acute Physiology Score III (APS III) scores, and Glasgow Coma Scale (GCS) scores. Additional data included information on the administration of ventilatory support and vasopressor. In-hospital mortality IHM served as the primary endpoint of the study.

2.4. Statistical methods

Categorical variables with category proportions less than 10% were excluded from the analysis. We eliminated variables with over 20% missing data and applied multiple imputations to estimate values for the remaining variables. Outliers were specified as values outside the range of 1%–99% and were addressed using winsorization. Means and standard deviations were determined for continuous variables, and t-tests were employed to compare the two groups. Moreover, skewed distributions were represented by medians and interquartile ranges, and Mann-Whitney U test was leveraged for comparisons. For categorical variables, counts and percentages were provided, and the χ^2 test was employed for group comparisons.

To examine the consequences of vitamin D intake on survival results, we utilized KM curves along with the log-rank test. Moreover, to estimate the link of mortality risk with vitamin D intake in RRT patients multivariable Cox regression models were employed. Model 1 did not account for any variables; Model 2 incorporated age, sex, and race as adjustment variables; Model 3 was adjusted for additional covariates age, sex, race, HR, RR, temperature, hemoglobin, WBC, platelet count, albumin, ALT, AST, TBIL, BUN, creatinine, venous blood glucose, lactate, pH, diabetes, chronic pulmonary disease, myocardial infarction, free calcium, phosphate, potassium, sodium, PT-INR, cerebrovascular disease, congestive heart failure, liver disease, kidney disease, malignancy, mechanical ventilation use, APS III, GCS, and SOFA scores.

To improve the reliability of the results, we performed PSM to address baseline differences between the groups. A 1:1 matching ratio was used with a matching window width of 0.1 times the standard deviation of the logistic regression probability score. This method ensured that patients in the vitamin D group were matched to those in the non-vitamin D group based on similar baseline characteristics, such as age, sex, race, vital signs, comorbidities, and severity scores. By balancing these covariates, PSM effectively reduced the influence of confounding variables, allowing for a more accurate comparison of outcomes between the two groups. To further evaluate the impact of vitamin D intake on specific populations, we also executed subgroup analyses with respect to age, sex, race, and the presence of the aforementioned comorbidities. This approach enabled the identification of potential interactions and

differential effects of vitamin D supplementation in various patient subgroups. Statistical assessments were undertaken using R software (version 4.3.3). A p-value below 0.05 was considered statistically significant. Through PSM, we addressed selection bias by constructing a pseudo-randomized control sample. The logistic regression model calculated propensity scores based on the likelihood of receiving vitamin D supplementation, accounting for key clinical and demographic variables. By creating a balanced dataset where matched pairs had comparable baseline features, we mitigated the effects of confounding factors that might otherwise distort the observed relationship between vitamin D intake and in-hospital mortality. Post-matching diagnostics, including standardized mean differences (SMD) and visual inspection of covariate balance, confirmed that the matched groups achieved a high degree of similarity, validating the robustness of our analytical framework.

3. Results

3.1. Baseline characteristics

In this study, 1270 patients who received RRT were analyzed. Based on vitamin D intake, they were classified into vitamin D and non-vitamin D groups with 338 and 932 patients, respectively. We excluded categorical variables with category proportions less than 10% and variables with more than 20% unavailable data (the excluded variables included MAP, SpO2, BNP, CRP, PTH, 25(OH)D, peripheral vascular disease, dementia, metastatic solid tumors, paralysis, AIDS, and the use of vasopressor drugs). The epidemiological characteristics, vital signs, laboratory indices, and comorbidities for the two groups are presented in **Table 1**. The vitamin D group demonstrated lower levels of HR, WBC, ALT, AST, TBIL, phosphorus, lactate, APS III score, SOFA score, a higher proportion of Caucasians, and a lower prevalence of diabetes. Additionally, the vitamin D group exhibited higher albumin, free calcium, pH values, and a higher prevalence of kidney disease. Concerning patient outcomes, the non-vitamin D group experienced an elevated probability of IHM.

Table 1. Baseline characteristics of the original population.

	Vitamin D (*n* = 338)	**No vitamin D (*n* = 932)**	***P***
Age (years)	63.0 [54.0; 72.0]	63.0 [53.0; 74.0]	0.737
Gender (*n*)			0.142
Male	198 (58.6%)	590 (63.3%)	
Female	140 (41.4%)	342 (36.7%)	
Race (*n*)			<0.001
White	211 (62.4%)	710 (76.2%)	
No White	127 (37.6%)	222 (23.8%)	
HR (beats/minute)	87.0 [73.0; 104]	91.5 [79.0; 109]	0.001
RR (breaths/min)	19.0 [16.0; 23.8]	20.0 [16.0; 24.0]	0.063
Temperature (°F)	98.0 [97.5; 98.7]	98.1 [97.5; 98.7]	0.831
Hemoglobin (g/dL)	11.9 (2.10)	11.8 (2.40)	0.337
WBC (K/uL)	7.30 [5.50; 10.1]	8.90 [6.30; 12.8]	<0.001

Table 1. (*Continued*).

	Vitamin D (*n* = 338)	**No vitamin D (*n* = 932)**	***P***
Platelet (K/uL)	204 [132; 277]	198 [133; 269]	0.592
Albumin (g/dL)	3.70 [3.10; 4.20]	3.30 [2.70; 3.90]	<0.001
ALT (IU/L)	26.0 [17.0; 48.0]	28.5 [18.0; 62.0]	0.017
AST (IU/L)	32.5 [21.0; 65.0]	42.0 [24.0; 112]	<0.001
TBIL (mg/dL)	0.60 [0.30; 1.30]	0.70 [0.40; 1.83]	0.001
BUN (mg/dL)	25.0 [16.0; 45.0]	27.0 [17.0; 45.0]	0.351
Creatinine (mg/dL)	1.30 [0.90; 2.20]	1.40 [1.00; 2.70]	0.086
Glucose (mg/dL)	116 [95.0; 163]	123 [97.0; 172]	0.268
Free calcium (mmol/L)	1.10 [1.03; 1.16]	1.08 [1.00; 1.15]	<0.001
Phosphate (mg/dL)	3.60 [3.00; 4.30]	3.90 [3.20; 5.00]	<0.001
Potassium (mEq/L)	4.40 [3.90; 4.80]	4.30 [3.90; 4.90]	0.819
Sodium (mEq/L)	139 [135; 141]	138 [135; 141]	0.108
PT-INR	1.20 [1.10; 1.50]	1.20 [1.10; 1.60]	0.03
Lactate (mmol/L)	1.70 [1.20; 2.30]	1.80 [1.30; 3.00]	0.004
pH value	7.38 [7.31; 7.44]	7.36 [7.27; 7.42]	<0.001
Ventilator use (*n*)	255 (75.4%)	713 (76.5%)	0.751
Diabetes (*n*)	215 (63.6%)	415 (44.5%)	<0.001
Myocardial infarct (*n*)	61 (18.0%)	174 (18.7%)	0.865
Congestive heart failure (*n*)	134 (39.6%)	344 (36.9%)	0.41
Cerebrovascular disease (*n*)	20 (5.92%)	77 (8.26%)	0.204
Chronic pulmonary disease (*n*)	98 (29.0%)	229 (24.6%)	0.128
Liver disease (*n*)	110 (32.5%)	302 (32.4%)	1
Renal disease (*n*)	194 (57.4%)	396 (42.5%)	<0.001
Malignant cancer (*n*)	47 (13.9%)	113 (12.1%)	0.454
APS III score	60.0 [47.0; 78.0]	70.0 [53.0; 89.0]	<0.001
GCS score	15.0 [15.0; 15.0]	15.0 [15.0; 15.0]	0.15
SOFA score	8.00 [5.00; 11.0]	10.0 [6.00; 13.0]	<0.001
In-hospital mortality (*n*)	12 (3.55%)	222 (23.8%)	<0.001

Table 1 presents the baseline characteristics of the study population and their results in comparison between the vitamin D and non-vitamin D groups, covering a wide range of demographics, clinical characteristics and biochemical parameters. Sample size (*n*) indicates the number of patients in each group. For continuous variables, data are presented as mean ± standard deviation (Mean ± SD) or median [IQR], reflecting trends in concentration and dispersion, respectively. For categorical variables, data are expressed as frequencies and percentages, reflecting the distribution of a characteristic across groups. *p* values were used to test the significance of differences between groups, with $p < 0.05$ indicating that the difference was statistically significant. For example, albumin levels were significantly different between the two groups ($p < 0.001$), suggesting that patients in the vitamin D group may have a better nutritional status or liver function. The specific meanings of the

abbreviations are given below: HR, heart rate; RR, respiratory rate; WBC, white blood cell; ALT, alanine aminotransferase; AST, asparate Aminotransferase; TBIL, total bilirubin; BUN, blood urea nitrogen; PT-INR, prothrombin time- international normalized ratio. The following tables are identical.

3.2. Survival analysis and cox regression model for IHM

KM survival curves demonstrated that the in-hospital survival rate was substantially greater in the vitamin D group ($P < 0.0001$), as depicted in **Figure 1**. In the unadjusted original model (Model 1), the probability of IHM was substantially reduced in the vitamin D group (HR 0.21; 95% CI 0.12–0.38; $P < 0.001$). However, in Model 2, which was controlled for age, sex, and race, vitamin D intake was linked to a reduced likelihood of IHM (HR 0.22; 95% CI 0.12–0.40; $P < 0.001$). Following the adjustment for various confounding factors in Model 3, Cox regression analysis showed that the relation between vitamin D intake and a reduced likelihood of IHM remained significant (HR 0.35; 95% CI 0.19–0.63; $P < 0.001$), as illustrated in **Table 2**.

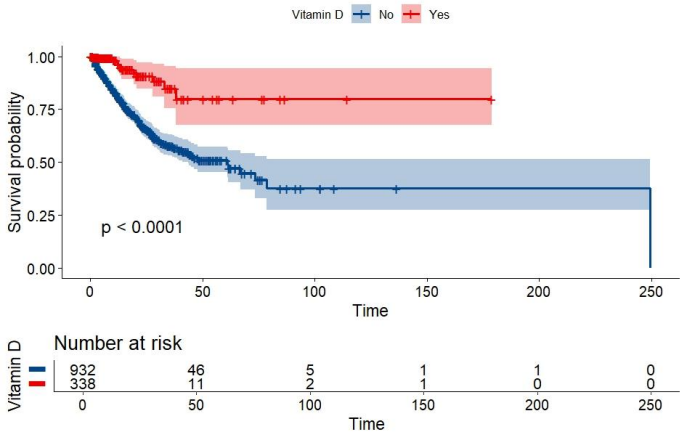

Figure 1. Kaplan Meier curve of in-hospital mortality risk in two groups for the original population.

Table 2. Results of cox proportional hazard models.

	Model 1		**Model 2**		**Model 3**	
	HR (95% CIs)	***p*-value**	**HR (95% CIs)**	***p*-value**	**HR (95% CIs)**	***p*-value**
In-hospital mortality						
No vitamin D	1		1		1	
Vitamin D	0.21(0.12, 0.38)	<0.001	0.22(0.12, 0.40)	<0.001	0.35(0.19, 0.63)	<0.001
PSM						
In-hospital mortality						
No vitamin D	1	1	1	1	1	1
Vitamin D	0.35(0.18, 0.66)	0.001	0.35(0.18, 0.66)	0.001	0.12(0.05, 0.29)	<0.001

The red curve indicates the probability of survival over time for patients who received vitamin D supplementation. The blue curve shows the survival probability over time for patients who did not receive vitamin D supplementation. The shaded

areas on either side of each curve represent 95% confidence intervals, which indicate the range of statistical uncertainty in the probability of survival. The narrower the shading, the more precise the estimate. The following figures are the same.

Model 1 covariates were adjusted for nothing. Model 2 covariates were adjusted for age, gender, and race. Model 3 covariates were adjusted for age, gender, race, HR, RR, temperature, hemoglobin, WBC, platelet count, albumin, ALT, AST, TBIL, BUN, creatinine, glucose, free calcium, phosphate, potassium, sodium, PT-INR, lactate, and pH value, diabetes, myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, liver disease, renal disease, malignant cancer, ventilator use, APS III, GCS, and SOFA. The specific meanings of the abbreviations are given below: PSM, propensity score matching.

3.3. Propensity score matching (PSM)

To handle confounding bias, we performed PSM according to vitamin D use. We successfully matched 315 pairs of patients, achieving balance in baseline features across the two groups, as shown in **Table 3**. The KM survival curve for the matched population showed trends consistent with the original cohort, as depicted in **Figure 2**. Similarly, we carried out multivariable Cox regression and linear regression analyses on the matched population. Following the adjustment for all confounders (Model 3), the vitamin D group demonstrated a substantially reduced likelihood of IHM (HR 0.12; 95% CI 0.05–0.29; $P < 0.001$), as presented in **Table 2**.

Table 3. Characteristics of the study population after propensity score matching.

	Vitamin D (*n* = 315)	**No vitamin D (*n* = 315)**	***P***
Age (years)	62.1 (13.8)	63.1 (14.0)	0.354
Gender (*n*)			0.744
Male	188 (59.7%)	193 (61.3%)	
Female	127 (40.3%)	122 (38.7%)	
Race (*n*)			0.868
White	205 (65.1%)	202 (64.1%)	
No white	110 (34.9%)	113 (35.9%)	
HR (beats/min)	90.1 (21.6)	89.9 (20.5)	0.904
RR (breaths/min)	19.7 (5.89)	20.0 (7.80)	0.584
Temperature (°F)	98.1 (1.30)	98.1 (1.75)	0.808
Hemoglobin (g/dL)	11.9 (2.09)	11.8 (2.19)	0.705
WBC (K/uL)	8.85 (6.49)	8.50 (4.04)	0.427
Platelet (K/uL)	213 (110)	212 (103)	0.935
Albumin (g/dL)	3.57 (0.74)	3.60 (0.67)	0.625
ALT (IU/L)	94.2 (350)	111 (400)	0.571
AST (IU/L)	126 (533)	175 (694)	0.326
TBIL (mg/dL)	2.14 (5.36)	1.93 (4.29)	0.576

Table 3. (*Continued*).

	Vitamin D (*n* = 315)	**No vitamin D (*n* = 315)**	***P***
BUN (mg/dL)	33.6 (25.7)	33.2 (23.3)	0.818
Creatinine (mg/dL)	2.17 (2.33)	2.28 (2.32)	0.563
Glucose (mg/dL)	150 (99.2)	151 (80.2)	0.839
Free calcium (mmol/L)	1.10 (0.15)	1.11 (0.24)	0.673
Phosphate (mg/dL)	3.88 (1.41)	3.94 (1.46)	0.604
Potassium (mEq/L)	4.43 (0.76)	4.40 (0.83)	0.627
Sodium (mEq/L)	138 (4.78)	138 (4.41)	0.979
PT-INR	1.53 (0.89)	1.51 (0.86)	0.743
Lactate (mmol/L)	2.23 (1.97)	2.22 (2.09)	0.978
pH value	7.36 (0.11)	7.36 (0.10)	0.641
Ventilator use (*n*)	235 (74.6%)	243 (77.1%)	0.515
Diabetes (*n*)	193 (61.3%)	198 (62.9%)	0.743
Myocardial infarct (*n*)	58 (18.4%)	58 (18.4%)	1
Congestive heart failure (*n*)	122 (38.7%)	136 (43.2%)	0.292
Cerebrovascular disease (*n*)	19 (6.03%)	19 (6.03%)	1
Chronic pulmonary disease (*n*)	91 (28.9%)	89 (28.3%)	0.93
Liver disease (*n*)	98 (31.1%)	97 (30.8%)	1
Renal disease (*n*)	172 (54.6%)	185 (58.7%)	0.335
Malignant cancer (*n*)	45 (14.3%)	40 (12.7%)	0.641
APS III score	64.5 (22.7)	64.3 (21.0)	0.874
GCS score	14.2 (2.44)	14.2 (2.41)	0.896
SOFA score	8.34 (4.33)	8.27 (3.95)	0.833
In-hospital mortality (*n*)	12 (3.81%)	46 (14.6%)	<0.001

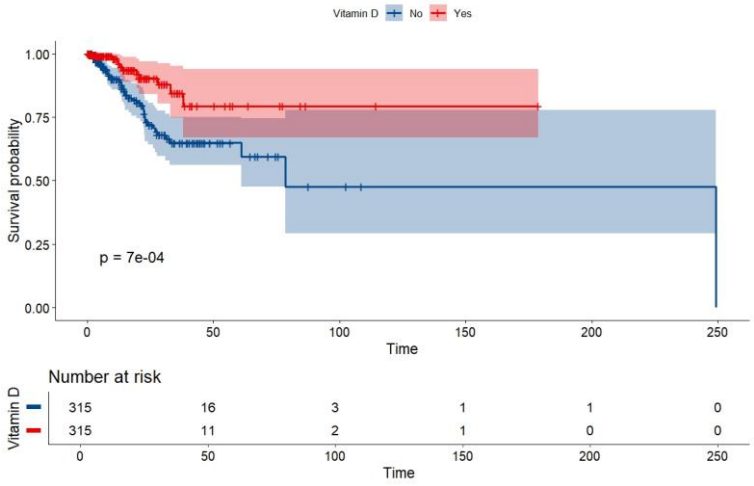

Figure 2. Kaplan Meier curve of in-hospital mortality risk in two groups for the PSM population.

Table 3 is a comparative table of the characteristics of the vitamin D-supplemented and non-supplemented groups after propensity score matching in this

study. The specific meanings of the abbreviations are given below: HR, heart rate; RR, respiratory rate; WBC, white blood cell; ALT, alanine aminotransferase; AST, asparate Aminotransferase; TBIL, total bilirubin; BUN, blood urea nitrogen; PT-INR, prothrombin time- international normalized ratio.

The figure is a Kaplan-Meier survival plot based on a propensity score-matched population to compare the risk of death during hospitalization in the vitamin D-supplemented group with that in the non-vitamin D-supplemented group.

3.4. Subgroup analysis

Subgroup analyses were carried out based on sex, race, age, and various comorbidities for IHM and length of stay, as illustrated in **Table 2**. A substantial interaction was observed between liver disease and the likelihood of IHM. Vitamin D intake had a substantial protective effect on patients with liver disease. No meaningful interactions were noted in other subgroups (interaction $P > 0.05$), as depicted in **Figure 3**.

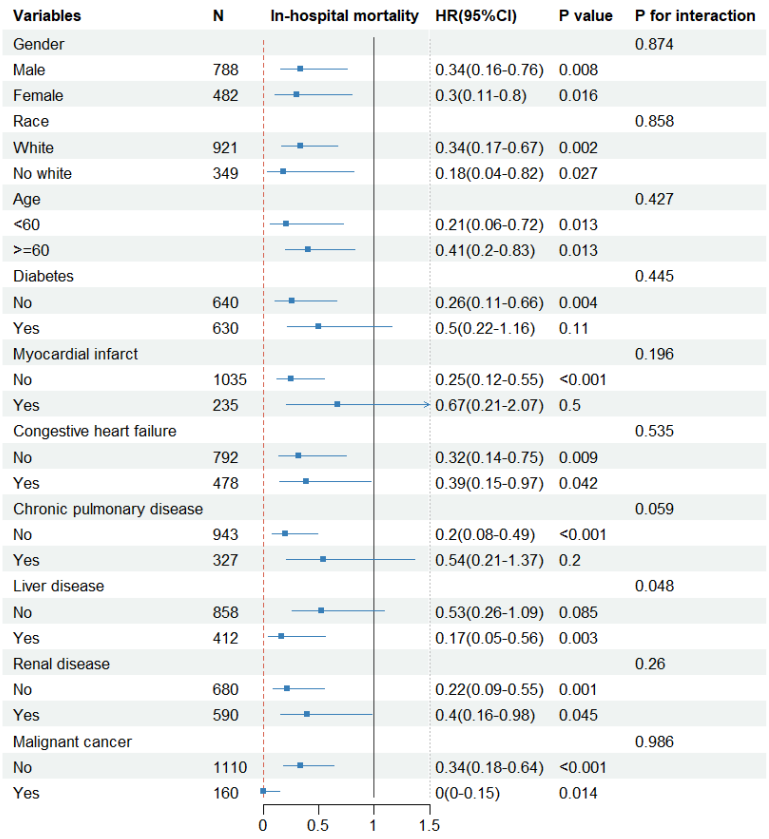

Figure 3. Subgroup analysis of the associations between in-hospital mortality and vitamin D received. Confounders were consistent with the model III in **Table 2**.

This figure is a forest plot showing the results of subgroup analyses to assess the effect of vitamin D supplementation on in-hospital mortality in a population with different characteristics. The range of the horizontal axis shows the values of the hazard ratios and their 95% confidence intervals. The red dashed line in the middle of the horizontal axis indicates the position where HR = 1, i.e., the null value. The vertical

axis includes different subgroup variables such as sex, race, age, chronic disease, and presence of malignant tumors.

4. Discussion

This large-scale retrospective cohort study determined that vitamin D intake was linked with a lower probability of IHM in ICU patients undergoing RRT. After adjusting for various factors and conducting PSM, this association remained significant, demonstrating the robustness of our results. To the extent of our knowledge, this is the first study to investigate the link of vitamin D intake with outcomes in ICU patients receiving RRT. These findings unveiled that vitamin D, as a low-cost and relatively safe approach, may improve the prognosis of these patients, offering a new direction for future clinical research. Further, the potential mechanisms underlying these observations warrant exploration, particularly in the influence of vitamin D on cellular and systemic biomechanics. Emerging evidence suggests that vitamin D plays a pivotal role in regulating cellular mechanotransduction, a process through which cells sense and respond to mechanical stimuli. By binding to the vitamin D receptor, vitamin D can modulate gene expression related to cytoskeletal organization and extracellular matrix interactions, potentially impacting pathways such as focal adhesion kinase and integrin signaling. These effects may enhance cellular resilience to mechanical stress, which is critical for maintaining tissue integrity in critically ill patients. In addition, vitamin D's role in muscle and skeletal biomechanics could partially explain its clinical benefits. Vitamin D facilitates calcium and phosphorus homeostasis, which is essential for bone mineralization and muscle contraction. Deficiencies in vitamin D have been linked to reduced bone stiffness and muscle weakness, both of which may increase the risk of complications such as fractures or impaired mobility. Improved biomechanical performance in muscle and bone could therefore contribute to the observed reduction in in-hospital mortality, as enhanced functional capacity supports recovery and reduces complications in ICU settings. Finally, the significance of vitamin D in modulating biomechanical dysfunction in liver disease and related complications is increasingly recognized. Liver disease is often accompanied by altered extracellular matrix remodeling and impaired vascular tension, processes that are regulated by mechanotransduction pathways sensitive to vitamin D. For example, vitamin D's anti-inflammatory and anti-fibrotic properties may mitigate mechanical stress on hepatocytes and vascular endothelial cells, thereby improving organ function and systemic hemodynamics. This may be particularly relevant in ICU patients with concurrent liver disease, as suggested by the subgroup analysis in this study.

Sunlight or ultraviolet radiation triggers the production of vitamin D in the skin (vitamin D3, also known as cholecalciferol), and it also can be acquired from dietary sources (vitamin D2, also known as ergocalciferol). The liver transforms vitamin D2 and D3 into 25(OH)D, which is subsequently converted in the kidneys to the active form, 1,25-dihydroxyvitamin D [2,11]. These forms of vitamin D attach to its receptors to produce their physiological effects. Vitamin D receptor, a nuclear receptor, is highly expressed in various tissues, including bones, muscles, liver, and immune cells, highlighting its broad physiological roles beyond calcium and phosphate

metabolism. VDR activation modulates numerous downstream signaling pathways, such as those involved in cell proliferation, differentiation, and apoptosis, thereby influencing systemic homeostasis. While the standards and definitions for vitamin D inadequacy differ across studies, low vitamin D levels are commonly seen worldwide [12]. The measurement of vitamin D levels is generally done by testing serum 25(OH)D [13]. Therefore, vitamin D deficiency is mostly defined as a 25(OH)D level below 20 ng/mL (50 nmol/L), with insufficiency defined as 21–29 ng/mL (52–72 nmol/L) and sufficiency as ≥30 ng/mL. According to these standards, it is believed that at least one billion individuals around the world experience vitamin D deficiency or insufficiency [2]. The prevalence of vitamin D inadequacy in adults ranges from 14% to 59%, with higher rates reported in Asian countries [14–16].

The physiological roles of vitamin D plays have been well-recognized, notably in calcium regulation and metabolism. Moreover, emerging evidence reveals that vitamin D contributes to cell proliferation and apoptosis, glucose metabolism, immune function, and inflammation [1]. Specifically, vitamin D influences cellular growth by modulating gene expression through the vitamin D receptor, which acts as a transcription factor upon activation. This regulation impacts critical pathways such as the Wnt/β-catenin pathway and TGF-β signaling, both of which are involved in cell cycle control and apoptosis. These mechanisms highlight the potential role of vitamin D in cancer prevention and tumor suppression. Research has shown that vitamin D inadequacy is linked to a greater likelihood of deaths in the general population [17]. However, the precise mechanisms behind this association are still unclear. Animal studies have demonstrated that mice missing the vitamin D receptor demonstrate various metabolic and cardiovascular disorders, along with a shortened lifespan [18]. Cardiovascular diseases, cancer, diabetes, and infectious diseases are major causes of mortality in developed countries [17]. Moreover, clinical studies have found that it is also a contributing factor for cardiovascular diseases [2,19,20].

In ICU patients, the prevalence of vitamin D inadequacy is high, although the exact rates vary across studies [3,21,22]. ICU patients with deficient vitamin D may arise from insufficient sun exposure, malnutrition, increased breakdown of vitamin D owing to inflammation, and decreased vitamin D-binding protein concentrations [23–25]. Additionally, critical illness itself may exacerbate vitamin D depletion through increased metabolic demands and impaired hydroxylation processes in the liver and kidneys, which are necessary for activating vitamin D. These physiological changes are further compounded by the frequent use of medications, such as glucocorticoids and anticonvulsants, that interfere with vitamin D metabolism. Moreover, numerous research has unveiled a relationship between low vitamin D concentrations and poor outcomes in ICU patients [6–8, 26–31]. For example, low vitamin D levels have been associated with increased rates of sepsis, acute respiratory distress syndrome (ARDS), and multi-organ failure, all of which are common causes of mortality in critically ill patients. Vitamin D's role in modulating immune responses and maintaining epithelial barrier integrity may partially explain these associations. However, the benefits of vitamin D intake in ICU patients are inconclusive [32–35]. A recent study of nine RCTs with a total of 1867 patients revealed no additional benefits of vitamin D intake relative to placebo in ICU patients [36]. This finding contrasts with a previous meta-analysis (seven trials, 716 patients), which has suggested that vitamin D intake reduced

mortality in ICU patients [37]. In 2014, Amrein et al. conducted the VITdAL-ICU trial (n = 475), where low vitamin D patients received a single high dose of 540,000 IU D3, followed by 90,000 IU monthly for five months. Their study revealed no substantial differences in hospital stay or mortality, but individuals with intense vitamin D inadequacy (≤12 ng/mL) in the intervention group showed a substantial reduction in IHM [38]. This indicates that specific patients may gain more benefits from vitamin D intake than others.

A study by Juntao Xie et al., which included 1,091 ICU patients, found that receiving RRT was a contributing factor for vitamin D insufficiency (OR 1.61, 95% CI 1.07-2.43) [5]. This may be linked to the loss of vitamin D and its binding protein during dialysis [39,40]. The molecular weight of 25(OH)D is 400 Da, making it easily cleared during dialysis. When 25(OH)D is coupled with vitamin D-binding protein, the molecular weight increases to 10 kDa, allowing it to be removed by convection [41], a form of RRT that can significantly reduce concentrations of both 25(OH)D and vitamin D-binding protein [42,43]. Additionally, studies have shown that dialysis filters with high binding capacity and cutoff qualities lead to amplified depletion of these substances [42]. Moreover, emerging evidence suggests that different RRT modalities, such as hemodialysis and hemodiafiltration, may exert varying impacts on vitamin D and its binding protein levels. For instance, high-flux membranes used in hemodiafiltration are particularly effective at removing middle and low molecular weight molecules, exacerbating the loss of vitamin D metabolites and associated proteins. However, the exact effect of RRT prescription parameters—such as dose, frequency, and duration—on vitamin D levels is still unclear. Regarding the substantial depletion of vitamin D in RRT patients, some researchers suggest that these patients might benefit more from vitamin D intake [44,45]. Our study supports this hypothesis and suggests that future interventional studies on the interplay of vitamin D intake pertaining to the prognosis of RRT patients should consider various dialysis prescriptions, including membrane type, dosage, frequency, and duration, as potential confounding factors.

Our subgroup analysis revealed an interaction across vitamin D intake, the presence of liver disease, and IHM in the Cox regression model. Vitamin D intake demonstrated significant protective effects in liver disease patients. A 2020 study involving 176 critically ill patients found that the mortality risk in subjects with low vitamin D (<10 ng/mL) was notably greater in individuals with cirrhosis compared to non-cirrhotic patients. This may be explained by the liver's crucial role in vitamin D metabolism [2,11]. Liver disease can interfere with the conversion of vitamin D to 25(OH)D, reduce the body's ability to cope with vitamin D deficiency, and increase the need for vitamin D [5,27], thereby leading to greater benefits in these patients. The liver is a central organ in vitamin D metabolism, as it catalyzes the first hydroxylation step, converting vitamin D into 25(OH)D, the main circulating form of the vitamin. In liver disease, particularly in advanced cirrhosis, hepatic dysfunction impairs this process, leading to reduced 25(OH)D levels despite adequate vitamin D intake. Additionally, liver disease is often accompanied by decreased production of vitamin D-binding protein and albumin, both of which are critical for the transport and bioavailability of vitamin D. These factors exacerbate the functional deficiency of vitamin D in patients with liver disease, rendering supplementation even more

essential. Furthermore, the anti-inflammatory and immunomodulatory properties of vitamin D may explain its protective effects in this population. Chronic liver disease is frequently characterized by systemic inflammation and immune dysregulation, both of which contribute to poor outcomes. By modulating cytokine levels and reducing oxidative stress, vitamin D supplementation may mitigate these pathological processes and improve overall prognosis. Emerging evidence also suggests that vitamin D might influence liver fibrosis progression through its role in stellate cell activation and extracellular matrix remodeling. Experimental studies have shown that vitamin D inhibits the activation of hepatic stellate cells, a key driver of fibrogenesis, thereby reducing collagen deposition and fibrotic scarring. This mechanism provides a biological rationale for the observed survival benefits in cirrhotic patients receiving vitamin D supplementation.

5. Conclusion

In conclusion, our study indicates that vitamin D intake is connected to a decreased likelihood of IHM in ICU patients undergoing RRT. This research uncovers the therapeutic effects of vitamin D for these patients, suggesting that clinicians should closely monitor vitamin D levels and consider supplementation when appropriate in clinical practice. Beyond its well-established role in calcium and phosphate homeostasis, vitamin D's impact on cellular and systemic biomechanics may contribute to its therapeutic potential. By modulating mechanotransduction pathways, such as integrin and focal adhesion kinase (FAK) signaling, vitamin D enhances cellular resilience to mechanical stress, which is particularly critical for tissues subjected to high hemodynamic and metabolic loads during RRT. Furthermore, the role of vitamin D in maintaining muscle and skeletal integrity, through its effects on bone mineralization and muscle contraction, may reduce complications such as frailty and mobility impairment in critically ill patients. However, the ultimate effectiveness of vitamin D intake should be confirmed through prospective, multi-center, randomized controlled trials. Future studies should also investigate the interplay between vitamin D supplementation and the biomechanical demands of RRT, including the effects of dialysis membrane type, frequency, and duration on vitamin D metabolism and patient outcomes. By integrating these biomechanical insights into clinical protocols, we can optimize vitamin D supplementation strategies to improve the prognosis of this vulnerable population.

Moreover, this study holds particular significance for specific subpopulations, such as patients with liver disease, as highlighted by the subgroup analysis. The findings revealed that vitamin D supplementation was associated with a significant reduction in in-hospital mortality (IHM) among liver disease patients. This is particularly noteworthy given the unique metabolic challenges faced by this population. Liver disease disrupts the conversion of vitamin D into its active forms due to impaired hepatic function, leading to profound deficiencies even in the presence of adequate dietary intake or sunlight exposure. Moreover, chronic liver disease is frequently accompanied by systemic inflammation, immune dysregulation, and a heightened risk of infections, all of which contribute to increased mortality risk. Vitamin D, with its immunomodulatory and anti-inflammatory properties, may

provide targeted therapeutic benefits by mitigating these pathophysiological mechanisms. Furthermore, the role of vitamin D in inhibiting hepatic stellate cell activation and reducing fibrotic progression adds an additional layer of relevance for patients with advanced liver disease, where fibrosis and cirrhosis are major determinants of prognosis. These findings underscore the potential for vitamin D supplementation to serve as a low-cost, accessible intervention to improve outcomes in this high-risk group.

There are several limitations to our study. First, due to its retrospective cohort nature, we were unable to obtain pre-treatment and post-treatment vitamin D levels for most patients. This limitation hindered our ability to assess the baseline severity of vitamin D deficiency and the extent of its correction after supplementation, which are critical factors in understanding its therapeutic efficacy. Second, although we made every effort to adjust for confounding factors, some potential confounders may still not have been accounted for. For instance, the concurrent use of other micronutrients, such as calcium or magnesium, which are often co-administered with vitamin D, may have influenced patient outcomes. These nutrients can modulate similar physiological pathways and may exert synergistic or independent effects on mortality and recovery, complicating the attribution of observed benefits solely to vitamin D. Additionally, unmeasured variables such as sunlight exposure, nutritional status, and the severity of systemic inflammation might have contributed to the outcomes but were not captured in the dataset. Third, our study primarily focused on the administration of vitamin D intake to patients and did not explore indications, types, dosages, or administration routes. The specific form of vitamin D (D2 vs. D3), its bioavailability, and pharmacokinetic differences can significantly affect its efficacy, yet these were not detailed in our analysis. Moreover, the lack of standardization in dosing regimens—ranging from bolus high-dose administration to smaller daily doses—introduces variability in the potential therapeutic effects observed. The method of administration (oral vs. intravenous) may also influence the speed and extent of vitamin D repletion, particularly in critically ill patients with compromised gastrointestinal absorption. These variations highlight the need for standardized protocols to ensure consistent and reproducible outcomes. Therefore, future prospective interventional studies should investigate the optimal timing, method, and dosage of vitamin D intake in ICU patients receiving RRT. Such studies should also aim to account for the interactions between vitamin D and other micronutrients, as well as evaluate the differential impacts of dosing strategies and administration routes on clinical outcomes. Furthermore, integrating biomarker-based monitoring, such as serial measurements of 25(OH)D and 1,25-dihydroxyvitamin D levels, could provide valuable insights into the dynamics of vitamin D metabolism in this population and help tailor supplementation protocols to individual patient needs.

This study underscores a significant association between vitamin D supplementation and improved outcomes in ICU patients undergoing RRT, laying the groundwork for future investigations. Validation through rigorous randomized controlled trials (RCTs) is essential to establish causality and refine clinical applications. Such trials should evaluate the optimal form, dosage, timing, and administration route of vitamin D, particularly addressing its interplay with RRT-related losses and baseline deficiencies. Comparative assessments of dosing strategies,

including high-dose boluses versus daily regimens, alongside the timing of supplementation relative to dialysis sessions, are critical to optimizing efficacy. Mechanistic studies are equally imperative to unravel the pathways through which vitamin D exerts its protective effects. These include its modulation of inflammatory processes, enhancement of cellular resilience via mechanotransduction pathways, and mitigation of complications such as muscle wasting and vascular dysfunction. Addressing potential confounders, including co-administered micronutrients, nutritional status, and systemic inflammation, will further strengthen the reliability of future findings. Personalized supplementation strategies, informed by serial biomarker monitoring of 25(OH)D and 1,25-dihydroxyvitamin D levels, hold promise for tailoring interventions to individual needs. Expanding research across diverse populations and multicenter settings will enhance generalizability and provide nuanced insights into subgroup-specific benefits, particularly for patients with comorbidities such as liver disease. Clinically, this study highlights the potential of vitamin D supplementation as an accessible, cost-effective intervention for critically ill patients, emphasizing the need for proactive monitoring and individualized therapeutic approaches. Addressing these research gaps will not only refine clinical protocols but also establish evidence-based guidelines for the optimal utilization of vitamin D in critical care.

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