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Vitamin D levels in patients admitted to the internal medicine intensive care unit and the association with mortality and other clinical outcomes

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ABSTRACT

Aim: To evaluate the effect of vitamin D levels on mortality and disease course in intensive care unit (ICU) patients.

Methods: This single-center retrospective study included 549 patients who had been treated in the Internal Medicine ICU of Kayseri City Hospital in the past year. The patients were divided into two groups according to their vitamin D levels. Patients with vitamin D levels less than 20 ng/ml were considered to have severe vitamin D deficiency (Group 1), whereas those with levels greater than 20 ng/ml did not have vitamin D deficiency (Group 2). The patients' 25-OH vitamin D levels, ICU stays, mortality status, and blood parameters were recorded.

Results: The median ICU stay durations of the studied patient groups were 4 (1–97) days in group 1 and 3 (1–17) days in group 2 (p<0.001). The patients' 25-OH vitamin D levels and ICU stay durations were negatively correlated (r=−0.863, p=0.005). The average 25-OH vitamin D levels were 17.2±11.07 ng/mL in the surviving group and 9.3±10.17 ng/mL in the nonsurviving group (p=0.043). The median C-reactive protein (CRP) values of the patient groups were 54.3 (0.2–398.4) mg/L in Group 1 and 87.5 (0.6–387.0) mg/L in Group 2 (p= 0.035).In the surviving group, the median Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 20.5 (14–34.5), whereas the median score in the nonsurviving group was 35.5 (30.5–52). Additionally, the median Sequential Organ Failure Assessment (SOFA) scores were 7 (5–10; p = 0.001) in the surviving group and 10 (6–12; p = 0.034) in the nonsurviving group.

Conclusions: The results of our study show that vitamin D deficiency is a common condition in critically ill patients admitted to intensive care and is associated with higher mortality rates and longer hospital stays. Supplementation with vitamin D may be considered as part of the recommended treatment for ICU patients.

Key words: 25-hydroxyvitamin D (25(OH) D, intensive care unit, vitamin D deficiency, mortality risk, sepsis, outcome.

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1. Introduction

Vitamin D, a fat-soluble nutrient, is essential in the regulation of calcium and phosphate metabolism. Insufficient vitamin D levels are acknowledged as a global public health concern. Although sun exposure is recommended for

vitamin D intake, many factors can affect the dermal synthesis of vitamin D. The prevalence of vitamin D deficiency in the general population ranges from 20% to 80% [1,2].

The primary sources of vitamin D include synthesis through sunlight exposure, dietary intake, and the use of vitamin D supplements. Vitamin D is typically present in limited quantities in food, often falling short of meeting the body's needs. When the skin is exposed to ultraviolet light, vitamin D undergoes conversion into 7-dehydrocholesterol and cholecalciferol, subsequently transforming into its active form, 1,25-hydroxy (OH) vitamin D3, in the liver and kidneys. It is then transported to various organs including the intestines, lungs, and bones by specific binding proteins for vitamin D. Simultaneously, tissues and cells with vitamin D receptors can express and host the active enzyme necessary for hydroxylation, resulting in the production of 1,25-OH D3.

Vitamin D regulates numerous physiological mechanisms, including cell differentiation, apoptosis, growth processes, and the modulation of inflammatory, immunomodulatory, and anticoagulant effects [3]. Vitamin D exerts regulatory influence over numerous physiological mechanisms, including cell differentiation, apoptosis, growth mechanisms, and the control of inflammatory, immunomodulatory, and anticoagulant effects [4]. Simultaneously, vitamin D can actively participate in conditions such as infectious diseases, autoimmune diseases, diabetes mellitus (DM), cardiovascular diseases, and cancer. Vitamin D insufficiency has been associated with cardiovascular diseases, metabolic syndrome, liver fibrosis, infections, coronavirus disease 2019 (COVID-19) infection, neurological disorders, and various cancers [5,6].

The positive effect of vitamin D on the immune system has been supported by various studies [3,7,8]. Research has been conducted, for example, on many chronic and autoimmune disorders such as multiple sclerosis, rheumatoid arthritis and type1 DM, which are linked to vitamin D deficiency, and a connection has been found [9-12]. It can also be said that vitamin D acts as an acute phase reactant and its level decreases in critical diseases. This study aimed to assess the prevalence of vitamin D deficiency in the intensive care unit (ICU) and investigate its association with acute diseases and mortality.

2. Materials and metods

Patients admitted to the Internal Medicine Intensive Care Clinic of Kayseri City Hospital, with documented vitamin D levels during hospitalization, were eligible for inclusion in this retrospective study. Through retrospective file review, 549 patients who underwent in patient treatment in the internal medicine ICU over the past year and met the study criteria were identified.

The study was conducted in accordance with the Declaration of Helsinki and patient rights regulations. All eligible participants were informed about the study's details, and both written and verbal consent were obtained from them. Research commenced after approval was granted by the Kayseri City Hospital Clinical Research Ethics Committee (Date: 2024.03.14 Decision no: 8).

Data concerning patients' clinical demographic characteristics and laboratory results were documented utilizing the hospital's information management system and archive files. Diagnoses, blood values, and vitamin levels at the time of hospitalization were recorded for each patient. At the same time, the number 9 of ICU stays, hospital stays, and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated. For patients with multiple

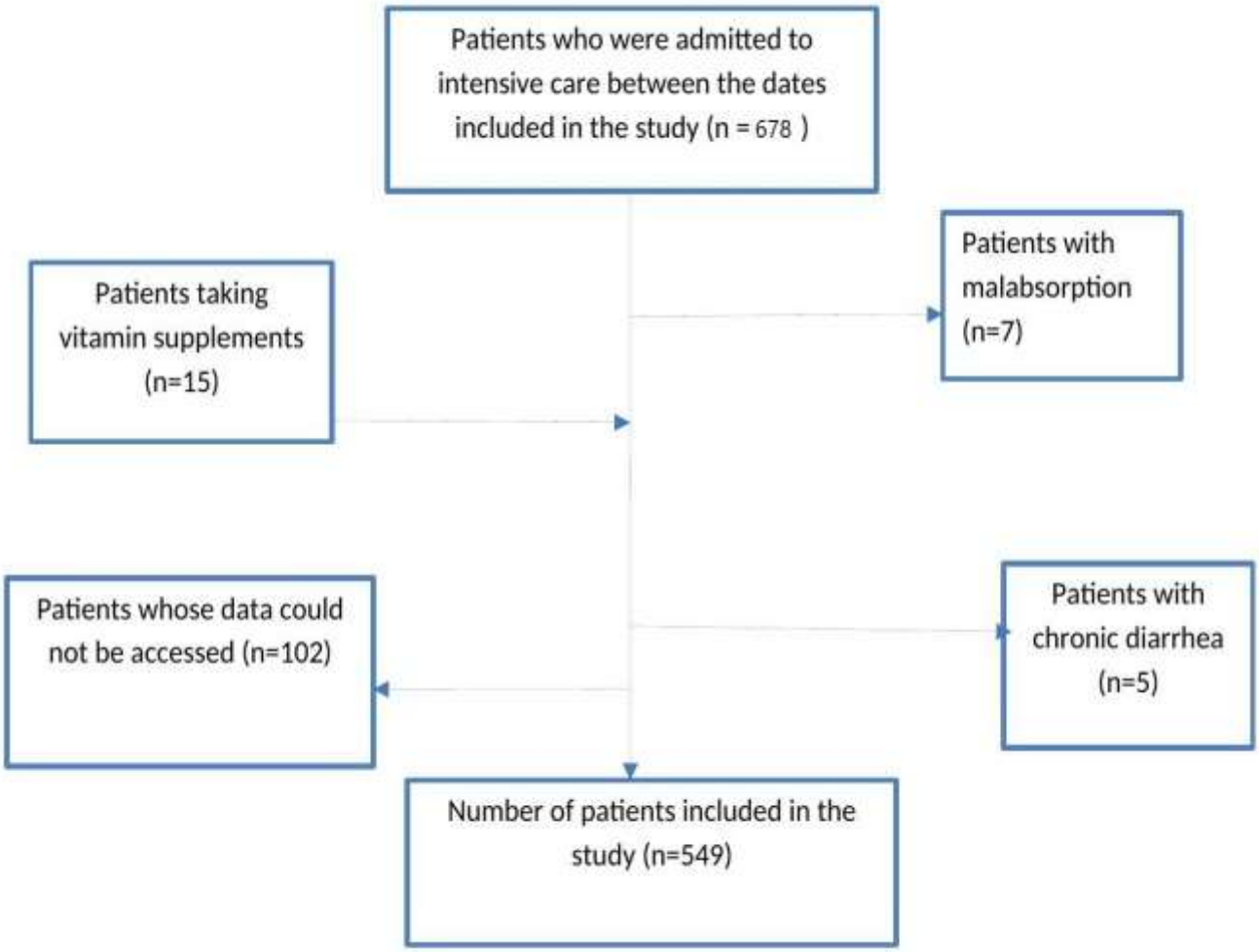

Figure 1. The flowchart of the patient selection process.

ICU admissions, only the initial hospitalization values were assessed. Among the criteria for excluding patients from the study: These include patients receiving multivitamin or vitamin D therapy, patients with malabsorption syndrome, patients with chronic diarrhea, and patients whose blood vitamin levels and data are not available (Figure 1).

The vitamin D level was assessed by measuring serum 25-OH vitamin D using ELISA. The patients were categorized into two groups based on their vitamin D levels: those with a vitamin D level <20 ng/ml were classified as having severe vitamin D deficiency (Group 1), while those with levels >20 ng/ml were categorized as not having vitamin D deficiency (Group 2).

2.1. Statistical analysis

All data analysis was conducted using IBM SPSS (Statistical Package for the Social Sciences) version 25. Normal distribution of variables was assessed through Kolmogorov-Smirnov tests, as well as graphical analysis. In analyzing the study data, normally distributed variables were presented as mean and standard deviation, while non-normally distributed variables were expressed as median and range. Independent T-test was employed for comparing normally distributed variables between two groups, while the Mann-Whitney U test was used

for non-normally distributed variables. One Way Analysis of Variance was utilized to compare normally distributed data among more than two groups, and the Kruskal Wallis Test was applied for non-normally distributed data. A significance level of $p<0.05$ was considered statistically significant for all tests.

3. Results

A total of 549 patients, 49.2% (n=270) female and 50.8% (n=279) male, were included in the study. There was no difference in gender distribution between the groups. The mean age of group 1 was 66.52±19.23 years, the mean age of group 2 was 70.63±17.50 years (Table 1). The median intensive care stay of the patients was 4 (1-97) days in group 1, 3 (1-17) days in group 2 ($p<0.001$). The median C- reactive protein (CRP) values of the patients were 54.3 (0.2-398.4) mg/L in group 1 and 87.5 (0.6-387.0) mg/L in group 2 ($p= 0.035$).

D deficiency, and 23% had adequate 25-OH Vitamin D levels. Severe vitamin D deficiency was observed in 85% of patients with acute kidney injury (AKI), and vitamin D levels were sufficient in 15%. Severe vitamin D deficiency was found in 75.4% of patients with oral intake disorders, and vitamin D levels were found to be sufficient in 24.6%. Additionally, 92.6% of patients with diabetic ketoacidosis had severe vitamin D deficiency and 7.4% had normal vitamin D levels (Table 2).

A strong negative (r: -0.863) and significant correlation was found between vitamin D level and ICU stay ($p = 0.005$) (Table 3). In the surviving group, the mean vitamin D level was found to be 17.2±11.07ng/mL, while in the non-surviving group, the mean vitamin D level was 9.3±10.17 ng/mL ($p=0.043$). In the surviving group, the median APACHE II score was calculated as 20.5 (14-34.5), whereas in the non-surviving group, it was 35.5 (30.5-52). Additionally, the Sequential Organ Failure Assessment Score (SOFA) score in the surviving group was 7 (5-10), compared to 10 (6-12) in the non-surviving group (p=0.001, $p=0.034$, Table 4).

Table 1. Comparison of demographic and clinical findings of the groups.

Parameters	Group 1 (n:445)	Group 2 (n:104)	*p*
Gender **Female** **Male**	217 (48.8%) 228 (51.2%)	53 (51%) 51 (49%)	0.790[a]
Age (years)	66.52±19.23	70.63±17.50	0.153[a]
Intensive care hospitalization Duration (days)	4 (1-97)	3 (1-17)	***<0.001***[b]
Procalcitonin (ng/mL)	1.2 (0.02-100)	1.08 (0.06-100)	0.467[b]
CRP(mg/L)	54.3 (0.2-398.4)	87.5 (0.6-387.0)	***0.035***[b]
Albumin (mg/dL)	28.76±7.51	27.99±7.18	0.853[a]
Lactate (mmol/L)	1.9 (0.5-23)	1.95 (0.8-12.5)	0.120[b]
WBC (10^3/µL)	11.53 (0.79-57.96)	13.49 (0.08-36.32)	0.094[b]

CRP: C reactive protein; WBC:White Blood Count; Values are presented as mean ±standard deviation or median (minimum-maximum) [a]: One Way Analysis of Variance [b]:Kruskal–Wallis Test

When the patients were evaluated according to clinical diagnoses, 84.9% of the patients with sepsis were found to have severe 25-OH Vitamin

Table 2. Evaluation of vitamin D deficiency according to patients' clinical diagnoses.

Parameters	Vitamin D	
	Deficiency (%)	Sufficiency (%)
Sepsis (n=152)	84.9	15.1
Acute kidney injury (n=120)	85	15
Oral intake disorder (n=53)	75.5	25.5
Diabetic ketoacidosis (n=27)	92.6	7.4

Table 3. Correlation evaluation between vitamin D deficiency and length of stay in intensive care unit.

		Intensive care stay
Vitamin D Deficiency	**Pearson r**	-0.863*
	p	***0.005***
	n	549

Correlation is significant at p<0.05 level.

the analysis of patient survival rates, it was evident that vitamin D levels were significantly lower in the non-survivor group.

The literature overwhelmingly supports the crucial Vitamin D's function within the immune system [13]. Vitamin D regulates the production of antimicrobial peptides in epithelial tissue, playing a role in defense against infection [14]. However, in addition to numerous studies showing the effect of vitamin D on the immune system, an experimental study has shown that vitamin D and inflammatory cytokines are not related [15]. Many studies conducted with sepsis patients have shown vitamin D deficiency [16]. The relationship between vitamin D and the immune system has also been supported by research [17]. Additionally, the relationship between many blood parameters indicating systemic inflammation and vitamin D levels has been demonstrated in the literature [18]. Our study revealed a significant deficiency of vitamin D in the majority of septic patients. The data obtained from our study are consistent with the relationship between sepsis and vitamin D in the literature. In another study involving 244 individuals, no significant relationship was found between 25-hydroxy vitamin D and CRP, leukocyte count, procalcitonin level, and blood culture positivity [19]. Similarly, in our study, no connection was found between leukocyte count

Table 4. Vitamin D level and survival analysis.

Parameters	Survivor (n: 337, 61.4%))	Non-survivor (n=212, 38.6%)	*p*
Vitamin D (ng/mL)	17.2±11.07	9.3±10.17	***0.043***[a]
APACHE II score	20.5(14-34.5)	35.5(30.5-52)	***0.001***[b]
SOFA score	7(5-10)	10(6-12)	***0.034***[b]

APACHE II score: Acute Physiology and Chronic Health Evaluation II Score, SOFA score: sequential organ failure assessment score. Values are expressed as mean ± standard deviation. Statistical significance (p < 0.05). [a]*: Independent samples t test.* [b]*: Mann–Whitney U test.*

4. Discussion

In this study, a significant difference was found in ICU stay durations among the groups categorized according to vitamin D levels. Additionally, a strong negative correlation was observed between ICU stay duration and vitamin D levels. Notably, the study highlighted a considerable deficiency in vitamin D among patients with sepsis, AKI, oral intake disorders, and diabetic ketoacidosis. Additionally, during

and procalcitonin level with vitamin D. However, a significant relationship was found between CRP and vitamin D levels.

Moromizato et al. in his study, it was shown that vitamin D levels before hospitalization were predictive of sepsis and increased mortality in critically ill patients [20]. Published articles consistently show that both 25-OH Vitamin D and 1,25-OH Vitamin D levels are lower in non-survivors among ICU patients [21]. In our study, 25-OH vitamin D levels of intensive care patients were evaluated. In our study, contrary to the findings in the study conducted by Cecchi et al., similar results were found with studies in the literature showing a relationship between vitamin D and mortality [22]. Likewise, our study identified a higher mortality rate among patients with low vitamin D levels.

In the literature, vitamin D deficiency rates of intensive care patients vary widely between 26% and 82% [16,23]. In our study, we observed that 61.9% of patients admitted to the ICU within a year had severe vitamin D deficiency, while 21.5% had mild to moderate deficiency. Research conducted by Matthews et al. revealed that surgical patients with insufficient vitamin D levels experienced prolonged ICU stays, elevated mortality rates, and heightened healthcare costs [24]. Similarly, our investigation unveiled an association between vitamin D levels and the length of ICU stay.

As shown in the study of Adams et al., considering the metabolic events in which vitamin D plays a role, organ dysfunctions may develop as a result of the increased need for vitamin D in an acute pathology [25]. The mechanism potentially linking vitamin D deficiency to the heightened risk of AKI in critically ill patients may be associated with the pleiotropic functions of vitamin D. Vitamin D inhibits the growth of vascular smooth muscle cells, supports endothelial function, and modulates inflammatory pathways [21]. In instances of vitamin D deficiency, macrophage function, encompassing phagocytosis, chemotaxis, and the production of proinflammatory cytokines, appears to be suppressed. In a study by Braun et al., it was discovered that pre-admission deficiency of 25-OH Vitamin D was associated with the risk of AKI in critically ill patients, independent of other risk factors [26]. Similarly, in this study, it was observed that a significant majority of patients admitted with AKI also had vitamin D deficiency.

The association between vitamin D and numerous chronic diseases has been explored. Numerous studies in the literature have linked vitamin D deficiency with conditions such as heart disease, hypertension, various cancers, DM, obesity, multiple sclerosis, rheumatological diseases, and respiratory diseases [9,12,27]. Similarly, in our study, we observed that the prevalence of vitamin D deficiency was high in patients with ketoacidosis, an acute disease associated with a chronic disease.

In geriatric patients, vitamin D deficiency primarily stems from reduced sunlight exposure, clothing habits, darker skin tones, and diminished skin synthesis of vitamin D [28]. In addition, vitamin D deficiency has been demonstrated in the literature in conditions with increased inflammatory burden, such as diabetes mellitus and sarcopenia [29,30]. Analogously, our study revealed a notable deficiency in vitamin D among patients admitted to intensive care due to oral intake disorders and electrolyte imbalances associated with Alzheimer's disease or prior cerebrovascular events. This reflects how important supplementary supports are in the geriatric population.

In critically ill patients, reduced levels of albumin, liver dysfunction, and consequently decreased levels of vitamin D binding protein are

frequently noted, even though levels of 25-OH Vitamin D may still be considered normal when free levels are within the normal range [31]. In our study, we noted that vitamin D levels in patients admitted due to oral intake disorders were relatively higher compared to other diseases, possibly due to lower albumin levels associated with oral intake disorders.

The retrospective design of the study, which precludes the evaluation of vitamin supplementation response in patients with vitamin D deficiency and the lack of post-admission control values, can be considered limitations of our study. Therefore, the results should be validated by prospective studies on a larger scale. Multicenter studies comparing diverse ethnic groups are needed to further explore the impact of vitamin D levels on sepsis and hospital outcomes.

4.1. Conclusions

Our results found that in addition to the high prevalence of vitamin D deficiency in ICU patients, vitamin D deficiency in critically ill patients is associated with poorer clinical outcomes affecting both survival and prolonged ICU stay. From a societal perspective, emphasizing the importance of vitamin and supplement supplementation and encouraging their widespread use may lead to a healthy lifestyle for public health.

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