Original Communication

Vitamin D deficiency and mortality among critically ill surgical patients in an urban Korean hospital

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Abstract: Critically ill patients in intensive care units (ICUs) are exposed to various risk factors for vitamin D deficiency. Vitamin D deficiency in extended-stay patients may result in decreased muscle mass and increased fat tissue, which may impair rehabilitation and recovery. Our study aimed to evaluate the degree of serum vitamin D deficiency in critically ill surgical patients and its association with clinical outcomes. Clinical data from 186 adult male (n = 121; 65.1%) and female (n = 65; 34.9%) patients hospitalized in surgical ICUs at Ajou University Hospital from April 2015 to September 2016 were retrospectively analyzed. All adult surgical patients between the age of 18 and 88 years were enrolled. The mean serum 25-hydroxyvitamin D (25[OH]D) level of all patients was 17.8 ng/mL. A total of 120 patients (64.5%) with serum 25(OH)D levels < 20 ng/mL were classified as the deficiency group. A prolonged hospital stay was observed among the deficiency group but was not statistically significant (p = 0.824). Serum 25(OH)D levels were significantly correlated with age but inversely correlated with Sequential Organ Failure Assessment (SOFA) score, selenium, triglycerides, and C-reactive protein levels. There was no significant difference in mortality rates between the group with a vitamin D injection and the group without a vitamin D injection (14.6% vs. 16.9%, p = 0.074). Vitamin D deficiency was common in surgical ICU patients; however, vitamin D levels were higher in older patients. In conclusion, vitamin D deficiency was inversely associated with the SOFA severity score (correlation coefficient −0.165, p = 0.024) but was not associated with the length of hospital or ICU stay and mortality.

Keywords: Vitamin D, deficiency, critical illness, mortality, outcome

Introduction

Vitamin D is essential for the maintenance of calcium homeostasis and bone and mineral metabolism [1]. Insufficient vitamin D increases the risk of osteoporosis and fractures [2]. Vitamin D deficiency causes rickets in children and osteomalacia in adults and serves as a risk factor for falling and impaired body function in vulnerable populations, including older adults [2–5].

Recent studies have found that vitamin D deficiency is related not only to bone metabolism but also to the occurrence of diabetes [6, 7], cancer [8, 9], cardiovascular diseases [10, 11], autoimmune diseases [12, 13], or infectious diseases such as tuberculosis [14]. In contrast, hypervitaminosis D causes hypercalcemia, calcification of soft tissues, and kidney and/or cardiovascular damage [15].

People living in countries in the upper northern hemisphere, such as Korea, are not exposed to sunlight strong enough to make vitamin D during the winter season. Additionally, with increasingly less time spent outdoors, there is a decrease in exposure to UV light which is essential for vitamin D synthesis. This leads to an increased risk of vitamin D deficiency.

The prevalence of vitamin D deficiency is high in certain populations depending on race, age, residential area, disease status, and culture [16]. Historically, the Institute of Medicine has defined vitamin D deficiency as a 25-hydroxyvitamin D (25[OH]D) level of $\leq$ 20 ng/mL, vitamin D insufficiency as a 25(OH)D level of 21–29 ng/mL, and vitamin D sufficiency as a 25(OH)D level of $\geq$ 30 ng/mL [17].

According to the National Health and Nutrition Survey conducted in Korea, only 13.2% and 6.7% of male and female participants, respectively, showed sufficient vitamin D levels (serum vitamin D level $\geq$ 30 ng/mL), and most of the remaining participants were deficient in vitamin D [18].

The United States National Health and Nutrition Survey also found that the percentage of people with vitamin D deficiency (serum vitamin D level <30 ng/mL) increased from 69% in 1988–1994 to 76% in 2001–2006 [19].

In addition, 17–79% of critically ill patients in intensive care units (ICUs) showed vitamin D deficiency [20–22]. Extended-stay ICU patients are exposed to various risk factors for vitamin D deficiency, including deficiency at the time of initial hospitalization, the use of restraints, the lack of proper exposure to the sun, malnutrition, infection, and liver and/or kidney dysfunction. In fact, the effects of vitamin D on the immune system, epithelial cells, glucose metabolism, and calcium homeostasis in critically ill patients are significant [16]. Vitamin D deficiency in long term patients may cause osteoporosis, immune dysfunction, or body composition changes (decreased muscle mass and increased fat mass) and may considerably impair rehabilitation and recovery [16]. Vitamin D deficiency has been found to increase the mortality rate among critically ill patients and the general public and is harmful for human health [16].

Our study aimed to determine the prevalence of vitamin D deficiency and its association with ICU disease severity scores, nutritional status, serum chemistries, micronutrients including zinc, selenium, copper, and manganese, and ICU clinical outcomes (length of stay, mortality) in a Korean cohort of surgical ICU patients. In addition, we investigated if a high dose of vitamin D given to patients would reduce mortality.

Subjects and methods

Participants and study design

This trial involved 186 adult patients (121 men, 65 women) hospitalized in surgical ICUs at Ajou University Hospital from April 2015 to September 2016. Because more men are admitted in the surgical ICU overall, we inevitably included more male than female subjects in patient selection and therefore this does not constitute selection bias. All adult surgical patients over 18 years old were enrolled. Pregnant or brain-dead patients were excluded. Our study was an open-label, prospective observational study. The Vitamin D injection portion of the study was a non-randomized, non-controlled trial. The vitamin D injection is a routine practice, administered to patients with low serum vitamin D levels (<30 ng/dL), and therefore, we did not intentionally manipulate vitamin D replacement. This study was approved by the Institutional Review Board of Ajou University Hospital (AJIRB-MED-MDB-17-358).

General characteristics

The sex, age, height, and weight of each participant were identified through the data recorded in electronic medical records. The body mass index (BMI, kg/m^2) was calculated based on the height and weight. In addition, using the guidelines of the Korean Society for the Study of Obesity (2000) for Asian adults, both male and female participants were classified as underweight (BMI: <18.5 kg/m^2), normal weight (BMI: 18.5–22.9 kg/m^2), and overweight or obese ($\geq$23.0 kg/m^2).

Severity scorings

Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA), and Simplified Acute Physiology Score III (SAPS III) were calculated based on the test results and clinical information within 24 hours after admission to the ICU.

Biochemical data analysis

25(OH)D, zinc, selenium, triglyceride (TG), prealbumin, copper, manganese, total bilirubin, albumin, and C-reactive protein (CRP) levels were analyzed using participants' blood samples collected from the radial arterial line during their ICU stay. Pre-albumin was analyzed with a Turbidimetric immunoassay (Kit: Roche Prealbmin, cobas 8000 c702 module) at GS Labs (Yongin, Kyeonggi-do, Korea). Zinc, Copper in serum, Selenium and Manganese in blood were analyzed using Inductively Coupled Plasma/Mass Spectrometry (Kit: House methods, Agilent 7700, Agilent, USA module) in Seoul Clinic Laboratories (Seoul, Korea). 25-OH Vitamin D was analyzed with Chemiluminescence immunoassay (Kit: ADVIA Centaur Vit.D Total (Vit.D), SIEMENS ADVIA Centaur XPT module), TG was analyzed using an Enzymatic Colorimetric test (Kit: Roche TRIGL, cobas c 702 module). Albumin and total bilirubin were analyzed with a Colorimetric assay (Kit: Roche ALB2, Roche Bilirubin Total Gen.3, cobas c 702 module) and CRP was analyzed using a particle enhanced immunoturbidimetric assay (Kit: Roche CRPL3, cobas c 702 module) in Ajou University Hospital, Laboratory medicine (Suwon, Kyeonggi-do, Korea).

Due to the high prevalence (>90%) of vitamin D deficiency in the general population, a great number of ICU patients are affected [23]. Based on the study, we classified the ICU participants into either deficiency (25[OH]D < 20 ng/mL) or non-deficiency (25[OH]D $\geq$ 20 ng/mL) groups.

Nutritional status assessment

Patients who are malnourished or at risk of being malnourished at the beginning of hospitalization may have longer hospital stays, more complications, and higher rates of mortality than well-nourished patients. Since malnutrition may vary in critically ill patients, nutritional status was assessed together as dietary intake and underlying diseases, which may be risk factors for malnutrition and may affect blood vitamin D levels. Hospitalized participants age, BMI, serum albumin level, symptoms of malnutrition (unintended weight loss for the past 1 month, dysphagia, difficulty in chewing, fasting for 3 days or more, loss of appetite for 2 weeks or more, and tube feeding), and high-risk diseases due to malnutrition (renal failure, liver cirrhosis, hepatic coma, congenital metabolic diseases, bedsores, multiple trauma, burn of 10% or more, and acquired immunodeficiency) were defined as risk factors for malnutrition. Subsequently, participants were divided into three groups: the low-, medium-, and high-risk groups for malnutrition. According to the assessment results, the low-risk group for malnutrition was indicated as "well nourished," and the medium- and high-risk groups for malnutrition were indicated as "malnutrition."

Statistical analysis

Statistical analysis was conducted on the collected data using SPSS Statistics version 18.0 software. We analyzed the normality of the variables using an F-test and found that some variables were not normally distributed. The mean and standard deviation of participants age, BMI, days of ICU stay, days of hospital stay, days of continuous renal replacement therapy (CRRT) use, days of ventilator use, severity scores (APACHE II, SOFA, SAPS III), zinc, selenium, TG, prealbumin, copper, manganese, total bilirubin, albumin, and CRP levels according to 25(OH)D levels were calculated, and a Mann-Whitney test was conducted. The frequency and percentage of sex, nutritional status, and future improvement distribution according to 25(OH)D levels were calculated, and a chi-square (χ^2) test was conducted. In addition, to examine the correlation between blood test parameters and severity scores according to 25(OH)D levels, Spearman's correlation analysis was performed. Also, Spearman's correlation values were calibrated to see if there was any relationship between Serum 25(OH) D level and other variables. Categorical variables were expressed as frequency and percentage, and continuous variables were summarized as mean ± standard deviation. The statistical significance of all results was defined as a p-value of < 0.05.

Results

Baseline characteristics according to serum 25(OH)D levels

The general characteristics of all participants are shown in Table 1. The mean age of all participants was 60.8 years, the mean BMI was 22.0 kg/m^2, and the mean serum 25(OH)D level was 17.8 ng/mL. More people were classified in the "malnutrition" group (60.8%) than the "well nourished" group (39.2%). There were no significant differences between male and female patients when comparing general characteristics. The main surgical departments with patients in the surgical ICU were general abdominal surgery (39.8%), liver transplantation (14.5%), and head and neck cancer surgery (10.2%). The reasons for the ICU admission was postoperative monitoring (55.4%), ventilator care (31.7%), hypovolemic shock (7.5%), and sepsis and septic shock (5.4%). The most common patient (29.6%) diet pattern was eating orally, then fasting due to surgery, then eating again after surgery, and leaving the ICU. Total parenteral nutrition (TPN) after surgery (23.7%), enteral nutrition with supplementary parenteral nutrition (19.9%), and oral diet after long term TPN (17.7%) followed.

Patients baseline characteristics and severity scores according to serum 25(OH)D levels are shown in Table 1. A total of 120 participants (64.5%) were classified into the deficiency group with serum 25(OH)D levels <20 ng/mL, and 66 (35.5%) into the non-deficiency group with serum 25(OH)D levels $\geq$ 20 ng/mL. There were no statistically significant differences between the groups at baseline. Severity scorings according to serum 25(OH)D level showed that the mean APACHE II, SOFA, and SAPS III scores were 18.8, 8.1, and 46.4 points, respectively, for the deficiency group. The scores for the non-deficiency group were lower (16.7, 6.8, and 43.0 points, respectively), the differences were statistically significant for SOFA scores ($p = 0.029$).

Total in-hospital mortality of the study population was 15.6% (29/186) and the in-hospital mortality of the vitamin D deficiency group (15.8%, 19/120) was not significantly higher than non-vitamin D deficiency group (15.2%, 10/66) ($p = 0.939$).

We further compared the mortality rate among patients according to vitamin D injection status (200,000 IU/time). A total of 83 participants received vitamin D injections (vitamin D injection group) and the remaining 103 participants did not receive a vitamin D injection (no vitamin injection group). Mortality rates for the vitamin D injection group (14/83, 16.9%) was slightly higher than that for the no vitamin D injection group (15/103, 14.6%). However, there was no significant

Table 1. Baseline characteristics according to serum 25(OH)D levels

Patient Characteristics	Total (n = 186; 100%)	Serum 25(OH)D level <20 ng/mL (n = 120; 64.5%)	Serum 25(OH)D level ≥20 ng/mL (n = 66; 35.5%)	p-value
Sex				0.793[3]
Men (No, %)	121 (65.1)	77 (64.2)[1]	44 (66.7)	
Women (No, %)	65 (34.9)	43 (35.8)	22 (33.3)	
Age (years)	60.8 ± 15.91	59.7 ± 16.46[2]	63.0 ± 14.76	0.118
BMI (kg/m^2)	22.0 ± 3.99	22.0 ± 3.82	22.1 ± 4.30	0.863
Serum 25(OH)D level (ng/mL)	17.8 ± 8.17	7.9 ± 2.40	20.4 ± 7.06	< 0.001***
Department (No, %)				0.912
General surgery	74 (39.8)	46 (38.3)	28 (42.4)	
Orthopedic surgery	13 (7.0)	8 (6.7)	5 (7.6)	
Head and neck surgery	19 (10.2)	12 (10.0)	7 (10.6)	
Trauma surgery	10 (5.4)	7 (5.8)	3 (4.5)	
Liver transplantation	27 (14.5)	20 (16.7)	7 (10.6)	
Others	43 (23.1)	27 (22.5)	16 (24.2)	
Reason for ICU admission (No, %)				0.713
Monitoring	103 (55.4)	64 (53.3)	39 (59.1)	
Hypovolemic shock	14 (7.5)	9 (7.5)	5 (7.6)	
Ventilator care	59 (31.7)	39 (32.5)	20 (30.3)	
Sepsis	10 (5.4)	8 (6.7)	2 (3.0)	
Type of nutrition (No, %)				0.281
Oral	55 (29.6)	39 (32.5)	16 (24.2)	
PN	44 (23.7)	31 (25.8)	13 (19.7)	
PN & EN	37 (19.9)	23 (19.2)	14 (21.2)	
PN & Oral	33 (17.7)	19 (15.8)	14 (21.2)	
EN & Oral	11 (5.9)	4 (3.3)	7 (10.6)	
EN	6 (3.2)	4 (3.3)	2 (3.0)	
Length of ICU stay (days)	13.6 ± 22.57	13.6 ± 24.01	13.5 ± 19.86	0.949
Length of Hospital stay (days)	44.3 ± 40.12	46.0 ± 44.13	41.1 ± 31.61	0.824
Length of CRRT use (days)	14.1 ± 11.43	13.1 ± 11.33	16.9 ± 12.14	0.353
Length of ventilator use (days)	17.1 ± 31.56	18.5 ± 36.32	14.6 ± 21.53	0.683
Nutritional status (No, %)				0.093
Well-nourished	73 (39.2)	42 (35.0)	31 (47.0)	
Malnourished	113 (60.8)	78 (65.0)	35 (53.0)	
Severity scores				
APACHE II	18.1 ± 8.08	18.8 ± 8.35	16.7 ± 7.43	0.155
SOFA	7.6 ± 5.52	8.1 ± 4.33	6.8 ± 4.77	0.029*
SAPS III	45.2 ± 17.40	46.4 ± 16.88	43.0 ± 18.23	0.186
In hospital mortality (No, %)	29/186 (15.6)	19/120 (15.8)	10/66 (15.2)	0.939
Mortality and Vitamin D injection				0.704
No injection (n = 103) (No, %)	15 (14.6)	11 (10.7)	4 (3.9)	
Injection (n = 83) (No, %)	14 (16.9)	8 (9.6)	6 (7.2)	

1) According to the χ^2-test.
2) Mean ± SD.
3) According to the Mann-Whitney test, * < .05.
Oral, Oral Diet; PN, Parenteral nutrition; EN, Enteral nutrition; 25(OH)D, 25-hydroxyvitamin D; BMI, Body Mass Index; 25(OH)D, 25-hydroxyvitamin D; ICU, intensive care unit; CRRT, continuous renal replacement therapy; APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II); SOFA, Sequential Organ Failure Assessment; SAPS III, Simplified Acute Physiology Score III.

Table 2. Serum 25(OH)D level by season of ICU admission

	Season of ICU admission				
Patient characteristics	Spring (n = 18; 9.7%)	Summer (n = 61; 32.8%)	Fall (n = 44; 23.7%)	Winter (n = 63; 33.9%)	p-value
Serum 25(OH)D levels (ng/mL)	18.1 ± 7.71[1)]	20.7 ± 9.12	16.1 ± 7.18	16.2 ± 7.34	0.010*[2)]

1) Mean ± SD; 2) According to Spearman's Correlation Coefficient, * < .05; 25(OH)D, 25-hydroxyvitamin D; ICU, intensive care unit

Table 3. Correlation between serum 25(OH)D levels and clinical outcomes

Classification	Age	BMI	Length of ICU stay	Length of Hospital stay	Length of CRRT use	Length of ventilator use	APACHE II	SOFA	SAPS III	
Serum 25(OH)D level	0.154[1)] (0.034*)	0.066 (0.366)	0.081 (0.272)	0.070 (0.343)	0.327 (0.103)	−0.001 (0.993)	−0.056 (0.451)	−0.165 (0.024*)	−0.106 (0.160)	
Classification	Zn	Se	TG	Pre	Cu	Mn	T.bil	alb	CRP	Ca
Serum 25(OH)D level	0.041 (0.584)	0.167 (0.026*)	−0.220 (0.004**)	0.071 (0.351)	−0.022 (0.767)	−0.057 (0.444)	−0.029 (0.688)	−0.067 (0.363)	−0.216 (0.003**)	−0.043 (0.558)

1) Spearman's Correlation Coefficient
* < .05, ** < .01.
25(OH)D, 25-hydroxyvitamin D; APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II); SOFA, Sequential Organ Failure Assessment; SAPS III, Simplified Acute Physiology Score III; Zn, Zinc; Se, selenium; TG, triglyceride; Pre, prealbumin; Cu, copper; Mn, manganese; T.bil, total bilirubin; alb, albumin; CRP, c-reactive protein; Ca, calcium.

differences between vitamin D supplementation and mortality regardless of the status of vitamin D (p = 0.704).

Serum 25(OH)D level by season of ICU admission

Serum 25(OH)D levels of all patients according to the season of ICU admission were analyzed as shown in Table 2. Serum 25(OH)D levels were higher among patients admitted to the ICU in the summer (20.7 ng/mL), followed by those admitted in the spring (18.1 ng/mL), winter (16.2 ng/mL), and fall (16.1 ng/mL) (p = 0.010).

Associations between serum 25(OH)D level and clinical outcomes

The association between serum 25(OH)D levels and general characteristics, severity scores, and blood test results is shown in Table 3. BMI, length of ICU stay, length of hospital stay, length of CRRT use, and length of ventilator use were positively, but not significantly, associated with serum 25(OH)D levels. However, serum 25(OH)D levels and age (r = 0.154, p = 0.034) showed a significant positive association with serum 25(OH)D levels. APACHE II (r = −0.056, p = 0.451), SOFA (r = −0.165, p = 0.024), and SAPS III (r = −0.106, p = 0.160) scores were negatively associated with serum 25(OH)D levels; however, only the association with the SOFA score was significant.

Zinc, selenium, prealbumin, and copper levels showed a positive association with serum 25(OH)D levels; however, only selenium (r = 0.167, p = 0.026) showed a significant positive association with serum 25(OH)D levels. In contrast, TG, manganese, total bilirubin, albumin, CRP, and calcium levels showed a negative association with serum 25(OH)D levels; however, only TG (r = −0.220, p = 0.004) and CRP (r = −0.216, p = 0.003) showed a significant negative association with serum 25(OH)D levels (Table 3).

Blood test results according to serum 25(OH)D levels

TG and CRP levels were significantly higher in the deficiency group than in the non-deficiency group (Table 4). Copper, manganese, total bilirubin, and albumin levels were considerably higher in the deficiency group than in the non-deficiency group. In contrast, selenium and prealbumin levels were considerably higher in the non-deficiency group than in the deficiency group.

Discussion

Our study evaluated the serum vitamin D levels of critically ill surgical patients and examined the relationship between serum vitamin D levels and clinical outcomes according to vitamin D status. In this study, the rate of vitamin D deficiency was high (64.5%) in patients in the surgical ICU. The mean serum 25(OH)D level of all patients was 17.8 ng/mL, which was lower than the threshold determined for the deficiency group (<20 ng/mL) according to the guidelines of the Institute of Medicine. A total of 120 patients (64.5%) were classified into the deficiency group with serum 25(OH)D levels <20 ng/mL. However, there was no significant correlation between vitamin D deficiency and the length of hospital or ICU stay and mortality.

Table 4. Blood test results according to serum 25(OH)D levels

	Serum 25(OH)D level		
Variables	<20 ng/mL (n = 120; 64.5%)	≥20 ng/mL (n = 66; 35.5%)	p-value
Zinc (μg/dL) (66.0–110.0)[1)]	59.5 ± 23.08[2)]	59.5 ± 23.45	0.830[3)]
Selenium (μg/dL) (5.8–23.4)	9.4 ± 2.76	10.2 ± 2.67	0.028
Triglyceride (mg/dL) (37.0–200.0)	104.8 ± 89.90	75.0 ± 48.14	0.004**
Prealbumin (mg/dL) (20.0–40.0)	11.0 ± 5.28	11.6 ± 4.70	0.230
Copper (μg/dL) (75.0–145.0)	87.4 ± 28.36	85.2 ± 32.08	0.341
Manganese (μg/L) (4.7–18.3)	11.3 ± 11.70	9.8 ± 3.62	0.242
Total bilirubin (mg/dL) (0.0–1.2)	2.9 ± 5.16	2.0 ± 2.87	0.188
Albumin (g/dL) (3.5–5.2)	3.1 ± 0.52	3.0 ± 0.44	0.197
C-reactive protein (mg/dL) (0.0–0.5)	10.3 ± 10.46	6.3 ± 7.17	0.006**
Calcium (mg/dL) (8.6–10.2)	8.0 ± 0.92	8.0 ± 0.81	0.924

1) Normal range; 2) Mean ± SD; 3) According to the Mann-Whitney test. * < .05, ** < .01. 25(OH)D; 25-hydroxyvitamin D.

Serum 25(OH)D levels were higher among participants admitted to the ICU during summer (20.7 ng/mL). Direct sunlight exposure was assessed by documenting the average duration of exposure and the percentage of the surface area of the body exposed daily [24].

Among our study population, age was significantly correlated with serum 25(OH)D levels. Our result is consistent with the results of a study by Kim et al. in critically ill patients [25]. Moreover, this is consistent with the results from a previous large-scale survey of Koreans reported that a lack of vitamin D is a serious health issue among young people [26]. The phenomenon of vitamin D deficiency in Korean youth appears to be directly related to industrialization. In Korea, young adults tend to gravitate toward urban areas and work primarily indoors, while older adults are more likely to live in rural areas and have outdoor jobs. This environmental difference may partially explain the phenomenon of greater vitamin D deficiency in the younger generation.

The mean length of ICU stay showed no significant difference between the deficiency and the non-deficiency groups. Total in-hospital mortality was 15.6% and the vitamin D deficiency group did not show higher mortality rates than the non-vitamin D deficiency group (15.8% vs. 15.2%). Previous studies, however, showed that vitamin D deficiency in critically ill patients was significantly correlated with a negative prognosis [25, 27–31]. According to a study conducted in the Netherlands in 2015 involving approximately 1,400 critically ill patients, the prevalence of vitamin D deficiency at the time of hospitalization was < 38%. According to that study, patients with vitamin D deficiency at the time of hospitalization showed higher severity scores and incidence rates of septicemia and a longer ICU stay but did not show significantly higher mortality [31]. In contrast, a study by Amrein et al. showed that 32% of all critically ill patients had low or very low vitamin D levels, and higher mortality was reported in these patients [27].

Analysis of serum 25(OH)D levels and severity scores showed that only SOFA was negatively correlated with serum 25(OH)D levels. One study showed that the vitamin D deficiency group had higher APACHE II scores compared to the normal vitamin D group among ICU patients [32]. Interestingly, our study also showed a significant relationship between vitamin D levels and SOFA scores, but not with other severity scores such as APACHE II and SAPS. However, we do not believe that the blood vitamin D levels in critically ill patients is a good marker of severity in ICU patients. The higher the severity scores, the more likely there is a vitamin D deficiency. Therefore, we suggest considering measuring vitamin D levels in the blood and actively supplementing them in patients with a deficiency. In comparison with the results by Kim et al. [16], the percentage of patients in the deficiency group was lower (87.8% vs. 64.5%) in our study, and serum vitamin D levels of all participants was higher (11.8 ± 7.9 ng/mL vs. 17.8 ± 8.17 ng/mL). This is likely because our study included critically ill surgical patients, while most participants in the study by Kim et al. were critically ill medical patients.

In addition, we found a significant negative correlation between both TG and CRP and serum 25(OH)D levels. Some clinical studies show that vitamin D deficiency is associated with certain inflammatory diseases and there is a mix of inverse and interrelated correlations between vitamin D deficiency and CRP [33]. Epidemiological studies suggest an inverse association between circulating levels of $25(OH)D_3$ and inflammatory markers, including CRP and interleukin (IL)-6 [34]. We also found statistically significant results between elevated TG and CRP and lower levels of vitamin D. These results might be associated with decreased intestinal calcium absorption and lower calcium

levels which can increase hepatic TG formation and secretion [35].

Our study indicated that with regards to hospital mortality, the group that did not receive the vitamin D injection tended to have higher mortality rates than the group that did receive the vitamin D injection. After a one-time intramuscular injection of 200,000 IU (cholecalciferol) patients were recommended to receive vitamin D injections every 3 months thereafter as the therapeutic effect was monitored, without exceeding 600,000 IU annually [36]. Vitamin D supplementation of 200,000 IU increased the concentration of 25(OH)D by a maximum of 20 ng/mL at 8 weeks after the intramuscular injection. However, according to independent studies, the occurrence of fractures or injuries from falling increased after vitamin D administration at a high dose of 300,000 or 500,000 IU; thus, it is necessary to be careful with the dosage of vitamin D [37]. Various studies have examined whether vitamin D supplementation in critically ill patients with vitamin D deficiency had significant effects on clinical outcomes. According to a meta-analysis by Langlois et al. of six randomized controlled studies conducted with 695 critically ill patients, vitamin D supplementation did not have a significant effect on the reduction of the length of ICU stay or mortality [38]. Berghe et al. also found that intravenous administration of vitamin D in long-term ICU patients did not lead to an increase in serum vitamin D levels [39].

In contrast, some studies have shown that active supplementation of vitamin D improved the status of patients. Putzu et al. conducted a meta-analysis of seven studies involving 716 critically ill patients. They showed that vitamin D supplementation, regardless of the dosage and administration duration (90,000–600,000 IU for 7 days to 6 months), decreased patient mortality with no serious side effects when compared with a placebo [40]. Luca et al. suggested the administration of a loading dose based on body weight and baseline 25OHD values to normalize vitamin D levels, while it was urgent to define the optimal regimen of vitamin D supplementation for maintaining normal levels, having a clear picture of daily vs. monthly administration, and low vs. high dosage [41].

Even if the supplementation dosage recommended for vitamin D deficiency in the general population is applied, the required dosage in critically ill patients may not be the same. Moreover, patients with renal failure, malabsorption syndrome, obesity, or patients using anti-seizure drugs require monitoring of their serum vitamin D levels and regulating alternative dosages accordingly [16]. Furthermore, more large-scale studies are necessary to identify the proper vitamin D supplementation dosage, subsequent effects, and side effects in critically ill patients.

There are some limitations to our study. This was a single-center study with a small number of participants. Due to the one-time measurement of serum vitamin D levels, it was not possible to measure changes in serum vitamin D levels during the ICU stay. In addition, most participants were critically ill surgical patients; therefore, they do not represent all critically ill patients. Although participants were injected with vitamin D at a dose of 200,000 IU once in this study, post-injection effects were not evaluated because the vitamin D test was not conducted due to the discharge of patients or excessive medical charges after the injection.

In conclusion, there was no significant correlation between vitamin D deficiency and the length of hospital or ICU stay and mortality. Also, Vitamin D replacement with 200,000 IU IV injection could not decrease the patients' hospital mortality. However, we suggest checking the serum Vitamin D level in selected ICU patients, such as malnutrition, long time bed-ridden status at home or nursery care center. And if necessary, providing adequate amounts of vitamin D is needed.

In the future, we need further studies with larger number of participants, long-term follow-up clinical outcomes in ICU patients with vitamin D deficiency. Furthermore, it is necessary to perform studies examining the effects and side effects of various methods of vitamin D supplementation in critically ill patients.

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Conflict of interest
The authors declare that there are no conflicts of interest.

Publication ethics
Our study includes human subjects. Our study was approved by the Institutional Review Board of Ajou University Hospital (AJIRB-MED-MDB-17-358).

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