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Efficacy and safety of enteral supplementation with high-dose vitamin D in critically ill patients with vitamin D deficiency

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ABSTRACT

Background: Vitamin D deficiency is associated with mortality and morbidity in critically ill patients. This study investigated the safety and effectiveness of enteral high-dose vitamin D supplementation in intensive care unit (ICU) patients in Asia.
Methods: This was a multicenter, prospective, randomized-controlled study. Eligible participants with vitamin D deficiency were randomly assigned to the control or vitamin D supplementation group. In the vitamin D supplementation group, the patients received 569,600 IU vitamin D. The primary outcome was the serum 25(OH)D level on day 7.
Results: 41 and 20 patients were included in the vitamin D supplementation and control groups, respectively. On day 7, the serum 25(OH)D level was significantly higher in the vitamin D supplementation group compared to the control group (28.5 [IQR: 20.2–52.6] ng/mL and 13.9 [IQR: 11.6–18.8] ng/mL, $p < 0.001$). Only 41.5% of the patients achieved serum 25(OH)D levels higher than 30 ng/mL in the supplementation group. This increased level was sustained in the supplementation group on both day 14 and day 28. There were no significant adverse effects noted in the supplementation group. Patients who reached a serum 25(OH)D level of >30 ng/mL on day 7 had a significantly lower 30-day mortality rate than did those who did not (5.9% vs 37.5%, $p < 0.05$).
Conclusions: In our study, less than half of the patients reached adequate vitamin D levels after the enteral administration of high-dose vitamin D. A reduction in 30-day mortality was noted in the patients who achieved adequate vitamin D levels.
Trial registration clinicaltrials.gov id: NCT04292873, Registered, March 1, 2020.

1. Introduction

Vitamin D plays crucial roles in bone metabolism, calcium homeostasis, and cardiovascular disease prevention [1]. Vitamin D also serves as a regulator of innate immunity, enhancing antimicrobial activity through mechanisms such as chemotaxis, autophagy, and phagolysosomal fusion within immune cells [2]. The potential immunomodulatory effects of vitamin D have been investigated in several chronic conditions associated with inflammation and the immune system, including diabetes [3], asthma [4], and autoimmune diseases [5]. Vitamin D deficiency in critically ill patients was published by Lee et al., in 2009 [6]. Scholars have often discussed the high prevalence of vitamin D deficiency (defined as a serum 25-hydroxyvitamin D (25(OH)D) level of <20 ng/mL) in intensive care unit (ICU) patients and its potential association with patient outcomes [7–10]. Vitamin D deficiency are significantly associated with mortality and high medical expenditure in critically ill patients [11–13]. Supplementation with a single high dose of oral vitamin D was demonstrated to elevate vitamin

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D levels without causing significant adverse effects [14]. However, several following randomized-controlled trials have obtained heterogeneous results regarding mortality and length of stay (LOS) [7,9,10,15,16].

Administration of the same loading dose of 540,000 IU to critically ill patients regardless of their baseline vitamin D levels and disease severity might be one possible explanation for the controversy. In addition, variations with region have been observed in the vitamin D levels in the general global population; vitamin D levels tend to be higher in North American regions than in other regions. Additionally, in the Asia/Pacific region, age-related differences in vitamin D levels were reported [17]. A multicenter study conducted in Asian populations demonstrated that more than half of critically ill patients had vitamin D deficiency and that 18% of these patients had severe vitamin D deficiency (defined as serum 25(OH)D level <12 ng/mL) [18]. However, limited clinical reference data are available regarding the effectiveness of vitamin D supplementation in changing serum vitamin D levels in ICU patients in Asian populations. This study investigated the efficacy and safety of enteral high-dose vitamin D supplementation in Asian ICU patients.

2. Methods

2.1. Study design and patient enrollment

We conducted a multicenter, prospective, randomized-controlled study from March 2020 to December 2022. This study was approved by the Research Ethics Committee of National Taiwan University Hospital (approval number: 201902073MIPA) and was registered on the ClinicalTrials.gov protocol registration system (www.clinicaltrials.gov, ID: NCT04292873). Written informed consent was obtained from each patient or their legal surrogate.

This study was conducted at 3 university-based teaching hospitals in northern Taiwan. Patients were recruited from medical and surgical ICUs. Patients who were 20 years or older; had serum vitamin D levels of less than 20 ng/mL; were receiving enteral nutrition; and had no history of ileus, vomit, or diarrhea were eligible for study participation. Patients who met any of the following criteria were not eligible to participate: age <20 years; having received high-dose vitamin D supplementation (>3000 IU/day) within 4 weeks of the study; having hypercalcemia (serum Ca level >2.6 mEq/L); body weight <45 kg or >90 kg; having been admitted to the ICU within 3 months; having a diagnosis of parathyroid disease, rickets, liver cirrhosis–Child C, renal stones, tuberculosis, or sarcoidosis [7]; and being a nonnative speaker of Mandarin.

Eligible patients were randomly assigned to either a control or vitamin D supplementation group at a 1:2 ratio. In the vitamin D supplementation group, the patients received enteral supplementation with **569,600** IU vitamin D (LiquiD P&B, 72,000 IU of vitamin D3 in 5 mL of coconut oil per bottle, Prime Health, Canada) either orally or through a feeding tube; they were administered a total of 8 bottles (1 bottle per hour). In the control group, the patients received standard critical care as per the protocol of each hospital. We did not mandate other clinical care, and the attending physicians were not informed of the patients' serum 25(OH)D levels at the time of each blood sampling. This approach ensured that this study was conducted without introducing any bias related to clinical decision-making based on vitamin D levels. In the 3 participating hospitals, routine high-dose vitamin D supplementation is not a standard practice, and patients typically receive vitamin D supplementation through regular daily nutrition only.

2.2. Patient grouping

For all study patients, the following demographic data and hemodynamic data were obtained from electronic medical records: age, gender, body mass index (BMI), Charlson comorbidity index (CCI) [19], sepsis diagnosis during enrollment, Sequential Organ Failure Assessment (SOFA) score [20], and Acute Physiology and Chronic Health Evaluation (APACHE) II score [21] obtained within 24 h of ICU admission; CCI scores are an indicator of various comorbidities (eg, malignancies, metastatic or hematologic malignancies, cardiovascular disease, renal insufficiency, hepatic insufficiency, stroke, respiratory insufficiency, and diabetes mellitus). The clinical outcomes, including LOS in the ICU, total hospital LOS, duration of ventilator use, and survival status, were monitored up to 90 days after patient enrollment. The adverse event of diarrhea (with the quantitative criterion set at more than 1000 g over 2 consecutive days) was recorded. The patients' serum calcium levels were monitored at the following time points: days 7, 14, 28, and 42 after their enrollment in the study. If the patient died or was unavailable upon discharge from the ICU or upon being discharged home, further blood sampling could not be obtained.

Most studies have defined the treatment goal for vitamin D deficiency as achieving serum vitamin D levels of 30 ng/mL or higher [17,22,23]. To evaluate the effectiveness of high-dose vitamin D supplementation and its impact on clinical outcomes in our cohort, we conducted exploratory analysis within the supplementation group. We categorized the patients into 2 subgroups on the basis of their serum vitamin D levels on day 7, with the subgroups comprising patients with levels above 30 ng/mL and levels lower than 30 ng/mL.

2.3. Primary outcome and exploratory analysis

The primary endpoint of our study was the serum vitamin D level on day 7 following study enrollment. Exploratory analysis of the serum vitamin D levels on days 14, 28, and 42 as well as the clinical outcomes of the critically ill patients was conducted.

After patient enrollment, blood serum samples were stored at −80 °C. The serum vitamin D level was measured using the commercial TOTAL Liaison chemiluminescence assay (Liaison, Diasorin S. p.A., Saluggia, Italy) [24]. The clinical outcomes included the 30-day and 90-day mortality rates, LOS in the ICU, total hospital LOS, presence of resistant bacterial infection after 30 days, and duration of ventilator use. We conducted comparisons to analyze these outcomes.

2.4. Statistical analysis

All numeric variables were assessed for normality by using the Kolmogorov–Smirnov test. Nonnormally distributed numerical data were compared using the Mann–Whitney *U* test and are expressed as medians and interquartile ranges (IQRs; Q1-Q3). Categorical variables were compared using the chi-square test or Fisher's exact test, where appropriate, and are expressed numerically and as proportions. The significance level was set at a 2-tailed *P* value of <0.05. All analyses were performed using the SPSS software package (IBM SPSS Statistics 22; IBM, Armonk, NY, USA).

3. Results

A total of 61 patients were enrolled in our study, with 41 patients included in the high-dose vitamin D supplementation group and 20 included in the control group (Fig. 1). The baseline demographics and characteristics of the enrolled patients are presented in Table 1. The baseline 25(OH)D levels were 14.05 ng/mL (IQR: 11.4–17.25 ng/mL). No significant difference was observed in age, gender, BMI, APACHE II severity score, SOFA score, CCI, initial diagnosis of sepsis, or albumin levels between the study and control groups.

3.1. Clinical outcomes and exploratory analysis

The main outcomes and exploratory analysis were shown in Table 2. The serum 25(OH)D level on day 7 was significantly higher in the vitamin D supplementation group than in the control group (28.5 [IQR: 20.2–52.6] vs 13.9 [IQR: 11.6–18.8], $p < 0.001$). Moreover, at the serial follow-up, the serum vitamin D levels on days 14 and 28 were all higher

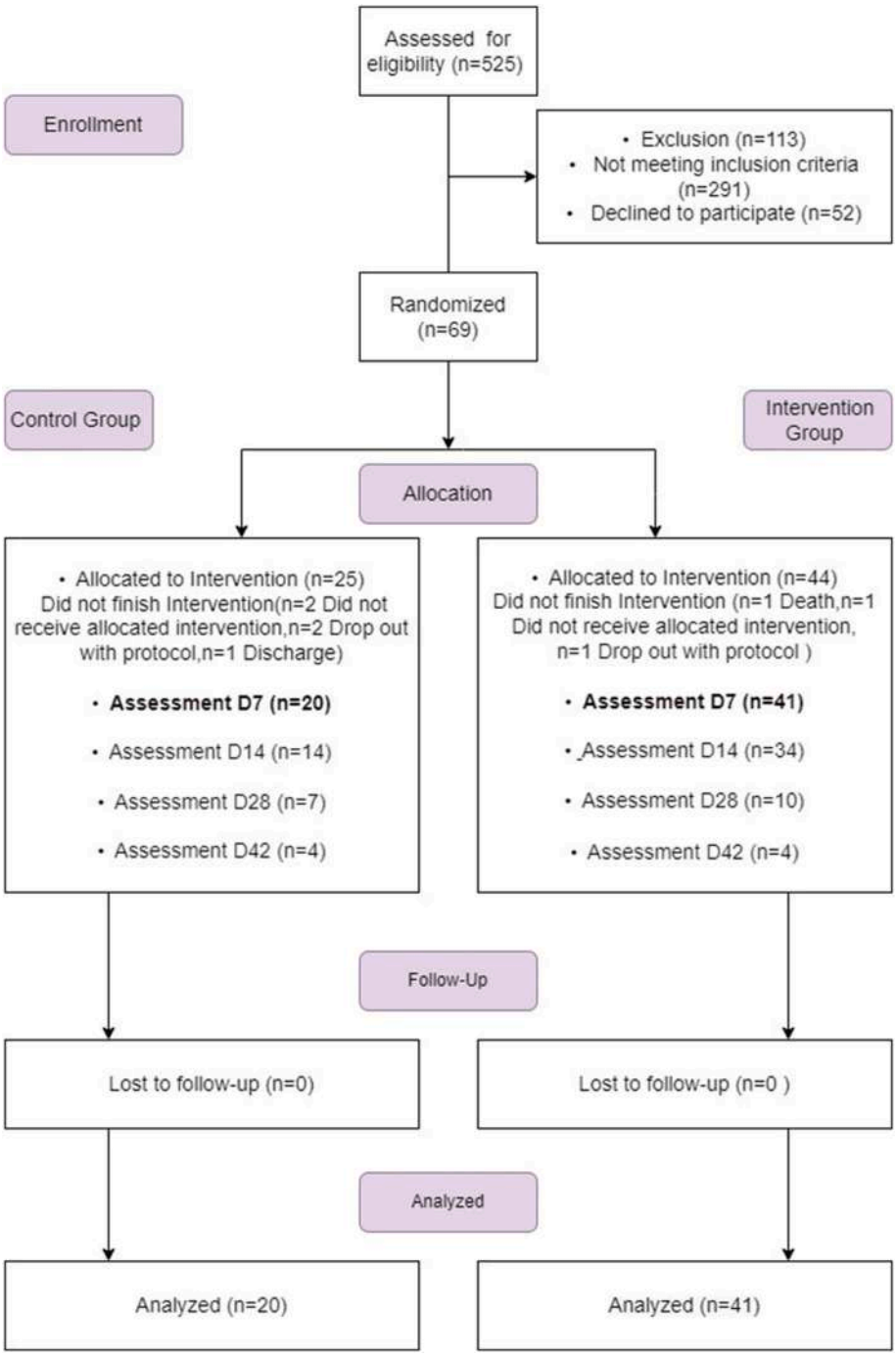

Fig. 1. Flowchart of patient enrollment and analysis. (D7, D14, D28, and D42 = days 7, 14, 28, and 42 after enrollment, respectively).

in the vitamin D supplementation group than in the control group (all $p < 0.05$). The median serum vitamin D level on day 42 in the vitamin D supplementation group was higher than that in the control group, although no significant difference was observed, likely due to the limited case number.

Exploratory analysis of the clinical outcomes revealed no statistically significantly difference in the 30-day or 90-day mortality between the vitamin D supplementation group and the control group (24.0% vs 15.0%, $p = 0.516$ for 30-day mortality; 36.6% vs 35.0%, $p = 0.904$ for 90-day mortality); the LOS in the ICU, and total hospital LOS were not significantly different between the groups (11.5 [IQR: 6.0–18.0] days vs 12.0 [IQR: 7.0–16.5] days, $p = 0.919$ for ICU LOS; 23.5 [IQR: 17.25–35.0] vs 30.0 [IQR: 15.0–55.5] days, $p = 0.387$ for total hospital LOS). No difference was observed in the duration of ventilator use. A lower rate of resistant bacterial infection was noted in the vitamin D supplementation group than that in the control group, but the difference was nonsignificant (26.8% vs 50.0%, $p = 0.074$). A higher percentage of patients in the vitamin D supplementation group had diarrhea, but the difference was nonsignificant (23.5% vs 5.3%, $p = 0.160$). No specific hypercalcemia was observed on day 7, 14, 28, or 42 between the 2 groups (Table 2).

3.2. Parameters related to serum 25(OH)D level on day 7 and clinical outcomes

In the vitamin D supplementation group, the median serum 25(OH)D

Table 1
Baseline characteristics of the studied patients.

Characteristic	*Vitamin D group (n=41)*	*Control group (n=20)*	p-*value*
Demographic			
Age – yr	71 (61–78)	65 (54–82)	0.438
Gender, male – no. (%)	27 (66%)	11 (55%)	0.412
BMI – kg/m^2	25 (21.8–26.4)	23 (21.3–26.3)	0.612
Clinical and illness severity at ICU admission			
APACHE II score	19.0 (14.0–24.0)	20.0 (15.5–25.5)	0.718
SOFA score	8.0 (4.0–9.0)	6.5 (4.8–8.3)	0.694
Charlson comorbidity index	3.0 (1.0–5.0)	1.5 (0–3.0)	0.060
Renal insufficiency or dialysis – no. (%)	7 (17%)	2 (10.0%)	0.704[a]
Clinical and illness severity at enrolment			
MAP – mmHg	85 (78–95)	85.5 (76.8–96.3)	0.908
Vasopressors use – no. (%)	10 (24%)	2 (10.0%)	0.305[a]
Mechanical ventilation – no. (%)	35 (85.4%)	16 (80.0%)	0.716[a]
ECMO – no. (%)	2 (4.9%)	1 (5.0%)	1.000[a]
Sepsis – no. (%)	14 (34.1%)	8 (40.0%)	0.655
Laboratory parameters at enrolment			
WBC - × 10^3/μL	10.2 (6.1–14.2)	11.1 (7.3–12.4)	0.830
Hb - g/dL	8.8 (8.2–9.9)	9.4 (8.7–10.2)	0.513
Hct - %	27.1 (24.2–30.6)	28.9 (26.4–30.8)	0.240
Platelet - × 10^3/μL	162 (82–234)	175.5 (129.0–249.5)	0.539
pH	7.41 (7.38–7.47)	7.45 (7.41–7.48)	0.176
PaO2 - mmHg	128 (110–146)	118.0 (90.5–149.3)	0.544
PaCO2 - mmHg	35 (32–39.6)	35.5 (31.4–37.7)	0.782
HCO3 - mEq/L	23.8 (21.1–26.3)	23.5 (20.6–25.9)	0.896
Creatinine - mg/dL	1.1 (0.7–2.4)	1.3 (0.5–2.0)	0.564
T-bilirubin - mg/dL	1.0 (0.6–1.7)	0.8 (0.5–1.1)	0.280
Albumin - g/dL	3.0 (2.8–3.3)	3.2 (3.0–3.5)	0.236
Na - mEq/L	137 (133–141)	138.5 (137.5–141.3)	0.190
K - mEq/L	3.9 (3.7–4.4)	3.9 (3.6–4.2)	0.450
Ca - mEq/L	2.09 (1.90–2.2)	2.1 (2–2.16)	0.583
P - mg/dL	1.0 (0.8–1.3)	1.3 (0.9–1.5)	0.212
25 (OH) D - ng/ml	**14.4 (11.5–17.1)**	**13.1 (11.0–16.8)**	**0.562**
Lactate - mEq/L	1.3 (1.0–2.0)	1.9 (1.2–2.4)	0.165
CRP - mg/dL	6.7 (3.4–8.8)	6.9 (3.5–12.9)	0.589

Values are expressed as either number of patients (%) or median (IQR, Q1-Q3). Abbreviation: BMI, body mass index; APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; MAP, mean arterial pressure; ECMO, extracorporeal cardiopulmonary support; WBC, white blood cell; Hb, hemoglobin; Hct, hematocrit; CRP, C-reactive protein.

[a] Fisher's exact test.

level on day 7 was 28.5 ng/mL (IQR: 20.2–52.6 ng/mL). In this study, 41.5% of the patients achieved serum 25(OH)D levels higher than 30 ng/mL on day 7. We divided the vitamin D supplementation group into 2 subgroups on the basis of their serum 25(OH)D levels on day 7, with one group having levels above 30 ng/mL and the other having levels lower than 30 ng/mL. No significant difference was found in the age, gender, BMI, baseline renal function, and albumin level between the 2 groups (Table 3). The patients with serum vitamin D levels above 30 ng/mL on day 7 had a higher platelet count (213 × 10^3/μL [IQR: 136–244] vs 123.5 × 10^3/μL [IQR: 75.5–204.5], $p = 0.021$) and lower potassium levels at enrollment (3.7 mEq/L [IQR: 3.5–3.9] vs 4.3 mEq/L [IQR: 3.9–4.8], $p < 0.001$). Patients with serum 25(OH)D levels above 30 ng/mL on day 7 had a higher initial serum 25(OH)D level at enrollment. Patients with serum vitamin D levels above 30 ng/mL on day 7 also had less severe illness severity scores (16.0 [IQR: 11.0–21.0] vs 21.0 [IQR: 17.0–26.3], $p = 0.032$ for APACHE II score; 5.0 [IQR: 3.0–8.0] vs 8.0 [IQR: 5.8–10.5], $p = 0.013$ for SOFA score). A higher rate of sepsis diagnosis was observed in the patients who not reach adequate serum 25 (OH)D levels on day 7, although this difference did not reach statistical significance (45.8% vs 17.6%, $p = 0.061$). The 30-day hospital mortality rate was lower for the patients with serum vitamin D levels above 30 ng/mL on day 7 than for those with levels below 30 ng/mL (5.9% vs 33.3%, $p = 0.028$). The 30-day survival curve between the control group and vitamin D supplementation group shown in Fig. 2. Detailed demographic characteristics of the 2 groups are listed in Table 3.

Table 2
Outcomes and Adverse effects for the total populations.

End points	*Vitamin D group (n=41)*	*Control group (n=20)*	p-*value*
Primary outcome: serum 25(OH)D level – ng/ml			
Day 7	28.5 (20.2–52.6)	13.9 (11.6–18.8)	<0.001
Exploratory analysis			
Serum 25(OH)D level at specific time point			
Day 14	N = 34	N = 14	
	32.5 (20.8–60.6)	14.7 (11.2–18.8)	<0.001
Day 28	N = 10	N = 7	
	45.2 (19.7–53.8)	13.9 (10.4–17.8)	0.008
Day 42	N = 4	N = 4	
	29.6 (22.2–36.8)	15.5 (12.5–17.5)	0.149
Clinical outcomes			
30- day mortality – no. (%)	10 (24%)	3 (15.0%)	0.516[a]
90- day mortality – no. (%)	15 (36.6%)	7 (35.0%)	0.904
ICU LOS after enrollment – days	11 (6–18)	12.5 (7–17)	0.890
Total LOS after enrollment – days	23.0 (17.0–35.0)	28.5 (15.5–54.8)	0.364
Resistant bacteria at 30 days – no. (%)	11 (26.8%)	10 (50.0%)	0.074
Duration of ventilator use – days	24.0 (0–26.0)	17.0 (4.8–24.5)	0.664
Adverse effects			
Diarrhea	8 (19.5%)	1 (5.0%)	0.249[a]
Ca level- mEq/L			
Day 7	N = 29	N = 11	
	2.10 (2.00–2.30)	2.10 (2.05–2.35)	0.521
Day 14	N = 21	N = 13	
	2.20 (2.20–2.30)	2.30 (1.90–2.40)	0.844
Day 28	N = 5	N = 5	
	2.30 (2.20–2.30)	2.20 (2.20–2.30)	0.585
Day 42	N = 0	N = 3	
	missing	2.30 (2.20–2.35)	–

Values are expressed as either number of patients (%) or median (IQR, Q1-Q3). Abbreviation: LOS, length of stay.

[a] Fisher's exact test.

4. Discussion

In this study, patients receiving vitamin D supplementation exhibited significantly elevated serum 25(OH)D levels, which remained elevated through day 28. Only 41.5% of the patients achieved serum vitamin D levels greater than 30 ng/mL on day 7 after receiving high-dose enteral vitamin D supplementation. No difference was observed in the 30-day or 90-day mortality between the vitamin D supplementation group and the control group. Furthermore, our study results indicated that the patients who reached adequate serum vitamin D levels on day 7 exhibited lower illness severity and higher baseline serum vitamin D levels. In our study, we also observed that the ability to attain the desired therapeutic target serum vitamin D level after supplementation is correlated with baseline vitamin D levels and illness severity.

Three factors were identified among patients who achieved adequate serum vitamin D levels on day 7, including lower illness severity scores, fewer sepsis diagnosis, and higher baseline vitamin D levels at enrollment. A higher severity of illness might be associated with greater vitamin D consumption, potentially resulting in lower vitamin D levels on day 7. Vitamin D levels were independently associated with sepsis severity [25]. Moreover, our exploratory analysis revealed that patients who achieved the therapeutic target (ie, vitamin D level above 30 ng/mL) had a lower mortality rate than did those with levels below 30 ng/mL. Thus, achieving a vitamin D level above 30 ng/mL may be associated with lower mortality. The dosage of vitamin D supplementation required to achieve a vitamin D level above 30 ng/mL warrants

Table 3
Parameters related to serum 25(OH)D level on Day 7 and outcomes in Vitamin D supplementation group.

Characteristic	Above 30 (n = 17)	Below 30 (n = 24)	*p*-value
Demographic			
Age – yr	68.0 (60.0–76.0)	73.0 (61.0–78.3)	0.534
Gender, male – no. (%)	10 (58.8%)	17 (63.0%)	0.424
BMI – kg/m^2	25.1(21.9–26.4)	25.0 (21.2–27.0)	0.832
Clinical and illness severity at ICU admission			
APACHE II score	16.0 (11.0–21.0)	21.0 (17.0–26.3)	0.032
SOFA score	5.0 (3.0–8.0)	8.0 (5.8–10.5)	0.013
Charlson comorbidity index	3.0 (1.0–4.0)	3.5 (1.0–5.3)	0.679
Renal insufficiency or dialysis – n (%)	14 (82.4%)	20 (83.3%)	1.000[a]
MAP – mmHg	87.0 (84.0–95.0)	80.5 (71.5–94.5)	0.090
Sepsis – n (%)	3 (17.6%)	11 (45.8%)	0.061
Vasopressors use – n (%)	4 (23.5%)	6 (25.0%)	1.000[a]
Mechanical ventilation – n (%)	13 (76.5%)	22 (91.6%)	0.212[a]
ECMO – n (%)	0	2 (8.3%)	0.502[a]
Laboratory parameters at enrolment			
WBC - × 10^3/μL	11.4 (6.8–13.5)	8.5 (6.1–14.5)	0.721
Hb - g/dL	9.2 (8.5–9.9)	8.5 (8.1–9.8)	0.361
Hct - %	28.3 (25.1–30.7)	26.0 (24.1–29.3)	0.347
Platelet - × 10^3/μL	213.0 (136.0–244.0)	123.5 (75.5–204.5)	0.021
pH	7.45 (7.41–7.48)	7.41 (7.38–7.44)	0.112
PaO2 - mmHg	138.0 (115.0–157.0)	126.0 (97.8–143.5)	0.186
PaCO2 - mmHg	34.8 (32.1–39.5)	35.0 (31.0–39.7)	0.822
HCO3 - mEq/L	24.3 (22.4–26.7)	23.3 (19.7–25.7)	0.341
Creatinine - mg/dL	0.9 (0.7–1.7)	1.5 (0.8–3.1)	0.208
T-bilirubin - mg/dL	0.9 (0.6–1.2)	1.0 (0.6–2.9)	0.552
Albumin - g/dL	3.1 (2.7–3.4)	3.0 (2.8–3.2)	0.953
Na - mEq/L	138.0 (133.0–143.0)	136.5 (132.8–141.0)	0.596
K - mEq/L	3.7 (3.5–3.9)	4.3 (3.9–4.8)	<0.001
Ca - mEq/L	2.05 (1.98–2.23)	2.09 (1.90–2.10)	0.416
P - mg/dL	0.9 (0.8–1.2)	1.1 (0.8–1.5)	0.372
25 (OH) D - ng/ml	15.7 (13.8–18.2)	13.6 (11.0–15.6)	0.055
Lactate - mEq/L	1.3 (1.0–1.9)	1.3 (1.0–2.0)	0.740
CRP - mg/dL	6.8 (4.9–7.7)	6.6 (2.2–10.7)	0.923
Endpoints			
30 days mortality – n (%)	1 (5.9%)	9 (37.5%)	0.028[a]
90 days mortality – n (%)	4 (23.5%)	11 (45.8%)	0.117
Resistant bacteria at 30 days – n (%)	4 (23.5%)	7 (29.2%)	0.736[a]
ICU LOS after enrollment – days	10.0 (4.0–18.0)	12.0 (6.5–20.5)	0.403
Total LOS after enrollment – days	21.0 (28.0–40.0)	18.0 (12.0–27.0)	0.536
Duration of ventilator use – days	21.0(25.0–29.0)	26.0 (23.5–29.3)	0.809

Values are expressed as either number of patients (%) or median (IQR, Q1-Q3). Abbreviation: BMI, body mass index; APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; MAP, mean arterial pressure; ECMO, extracorporeal cardiopulmonary support; WBC, white blood cell; Hb, hemoglobin; Hct, hematocrit; CRP, C-reactive protein.

[a] Fisher's exact test.

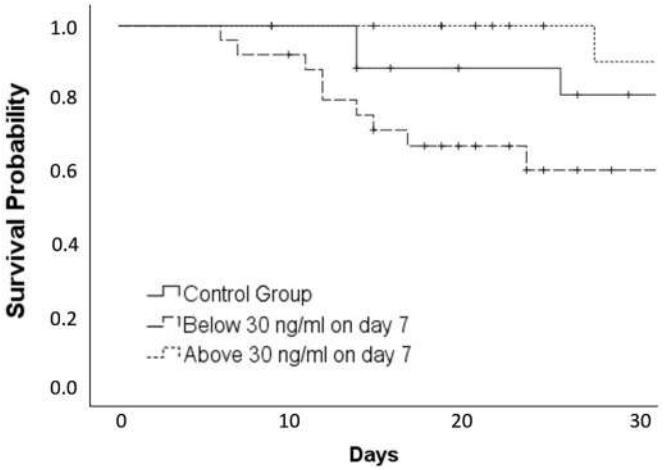

Fig. 2. The 30-day survival curve between the control group and vitamin D supplementation group. In the vitamin D supplementation group, patients were divided into 2 subgroups according to whether their vitamin D level was above or below 30 ng/mL on day 7. (n = 20 for control group, n = 24 for <30 ng/mL group, and n = 17 for >30 ng/mL group).

further investigation. Furthermore, we observed a lower incidence of resistant bacterial infections in the vitamin D supplementation group than that in the control group. This phenomenon could be attributed to the potential antimicrobial effects associated with vitamin D.

The dose of vitamin D (569,600 IU) supplement in this study was slightly higher than that in previously published protocols (540,000 IU). Despite this higher dose, only 41.5% of our patients achieved serum vitamin D levels above 30 ng/mL on day 7, which is lower than the percentages in the VITdAL-ICU trial (52%) [7] and the VIOLET trial (75.2%) [9]. In addition to ethnic differences, other differences may exist between the population in our study and those of these 2 other studies. First, the patients of our study were older and exhibited higher illness severity compared with those in the 2 aforementioned studies. Second, more than 80% of the patients underwent mechanical ventilation in our study, which is higher than the percentages of 60% in the VITdAL-ICU trial and 30% in the VIOLET trial. Third, 34.1% of the patients in the vitamin D supplementation group in our study were given a diagnosis of sepsis, which is higher than the percentage in the VITdAL-ICU trial (8%) and comparable to that in the VIOLET trial (34.4%). Further explorative studies are required to identify a supplementation protocol that can achieve a target baseline vitamin D level for individual patients. Furthermore, it's important to note that the emerging evidence indicates that large bolus doses of vitamin D may provide limited benefits or might be detrimental in specific scenarios, such as among various populations and for different purposes. In contrast, smaller to moderate daily doses are beneficial for individuals at risk of deficiency in those scenarios [26,27].

No serious adverse events were observed in our study. We demonstrated that high-dose vitamin D administration through the enteral route reasonably achieved the therapeutic target without causing significant adverse events. The highest serum 25(OH)D level recorded was 149 ng/mL on day 14. The occurrence of the adverse event of diarrhea was higher in the vitamin D supplementation group; however, this difference was nonsignificant. No specific life-threatening incidents related to hypercalcemia were reported in this study. Personalized vitamin D supplementation strategies should be implemented to optimize the effectiveness of vitamin D treatment.

Our study has several limitations. First, the small sample size limited the power to detect differences between the 2 groups in the exploratory analysis results. Second, most patients were discharged within 28 days; thus, less data on vitamin D levels were available after 28 days. Third, patients enrolled in the study were admitted to the ICU at different time points. It cannot be concluded whether the early or late administration of vitamin D in critical illness is effective. However, our study emphasizes the importance of tailoring vitamin D supplementation strategies based on individuals' baseline serum vitamin D levels and the severity of their illness. Further studies are warranted to investigate whether additional vitamin D supplementation for patients who do not achieve the therapeutic target can reduce mortality.

5. Conclusions

Less than half of our patients achieved adequate vitamin D levels after enteral high-dose vitamin D administration. Our exploratory findings show that vitamin D supplementation reduced resistant bacterial infections and hospital morality. Currently, the VITDALIZE trial, a multicenter study targeting critically ill patients with severe vitamin D deficiency, is underway [28]. This trial involves administering a loading dose to patients, followed by a daily maintenance dose. The outcomes of this trial are expected to offer additional insights into effective vitamin D dosing strategies. Additional research is needed to determine the optimal dosage, timing, and therapeutic objectives of vitamin D supplementation for critically ill patients in Asia.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Research Ethics Committee of National Taiwan University Hospital (approval number: 201902073MIPA). Written informed consent was obtained from each patient or their legal surrogate.

Declaration of competing interest

The authors declare that they have no competing interests.

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Abbreviations

25(OH)D	25-hydroxyvitamin D
APACHE II	Acute physiology and chronic health evaluation II
BMI	Body mass index
CCI	Charlson comorbidity index
ICU	Intensive care unit
IQR	Interquartile range
LOS	Length of stay
SOFA	Sequential Organ Failure Assessment

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