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Vitamin D Supplementation in Mechanically Ventilated Patients in the Medical Intensive Care Unit

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Abstract

Background: The utility of vitamin D (VITD) supplementation during critical illness and whether it may alter outcomes, including mortality and ventilator-free days, is unclear. We performed a retrospective cohort study in a generalizable population to investigate this question. *Methods:* We included all mechanically ventilated adults admitted to the medical intensive care unit (ICU) service at a tertiary center from 2009 to 2012 who were in the ICU for at least 72 hours. Patients were grouped as having received or not received VITD at any time during the first 7 days of their ICU stay, and we adjusted for the following covariates with multivariable analyses: simplified acute physiology score, age, gender, admission diagnosis, race/ethnicity, admission season, admission day of the week, and VITD supplementation prior to admission. *Results:* Among the 610 included patients, 281 received VITD, and 329 did not. There were no differences in outcomes between these groups. However, we did find significantly more ventilator-free days (21.0±2.6 [adjusted mean days±standard error] vs 17.6±2.4, P=0.04) and ICU-free days (18.5±2.5 vs 16.3±2.3, P=0.03) in patients who were taking VITD prior to admission (n=91) vs those who were not (n=519). No patients who were taking VITD before admission died vs 34.5% of those who were not (estimated odds ratio=4.9×10^{-7}, 95% CI=3.1×10^{-7} to 7.5×10^{-7}, P<0.0001). *Conclusion:* These results suggest that VITD supplementation during critical illness may not provide benefit and that further research investigating potential supplementation in ambulatory patients at high risk of ICU admission (eg, severe underlying chronic disease) is warranted. (*JPEN J Parenter Enteral Nutr.* 2019;00:1–7)

Keywords

critical care; mechanical ventilation; research and diseases; vitamin D

Clinical Relevancy Statement

Vitamin D supplementation that is initiated after critical illness has begun may not be beneficial, but supplementation before severe acute illness may be helpful in improving outcomes. These findings are clinically relevant for guiding clinicians who provide care either in medical intensive care units (ICUs) or for ambulatory patients who have a high risk of ICU admission.

Background

Vitamin D (calcitriol) is a fat-soluble vitamin necessary for regulating calcium, phosphorus, and bone metabolism, as well as other critical biological functions.[1-3] Humans obtain vitamin D_2 and D_3 from food and dietary supplements, and D_3 also comes from conversion in the skin from previtamin D_3, with exposure to sunlight.[4] Regardless of the source, vitamin D_3 is subsequently metabolized in the liver to

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25-hydroxyvitamin D_3 [25(OH)D; the circulating inactive form used to determine vitamin D status], then in the kidney to its active form, 1,25-dihydroxyvitamin D_3 (also called calcitriol).[5] Beyond its traditional role in regulating calcium, phosphorus, and bone metabolism, calcitriol has been found to play a vital role in the function of the innate and adaptive immune systems.[6] Vitamin D receptors are expressed in myriad cells and tissues such as T cells, dendritic cells, and activated B cells.[7-9] Vitamin D deficiency is associated with reduced macrophage chemotaxis and phagocytosis.[10] In critically ill patients specifically, decreased circulating levels of 25(OH)D are strongly associated with mortality, which might be explained by low 25(OH)D levels also being highly associated with reduced levels of cathelicidin-associated protein, a key factor of innate immune activation against pathogens.[11] Worldwide, up to 1 billion people are either deficient or insufficient in 25(OH)D, including the vast majority of the elderly population in the United States and Europe, as well as 50% of postmenopausal women.[12] Though deficiency is frequently attributed to low intake of foods fortified with vitamin D_3 and inadequate exposure to sunlight, low 25(OH)D levels can also be caused by chronic disease states, such as those associated with malabsorption and with autoimmune disease.[13]

Deficiency of 25(OH)D can lead to significant morbidity, including osteoporosis, osteomalacia, and rickets in children.[14] Interestingly, low 25(OH)D levels have also been associated with worsening outcomes in patients with cancer[15] and with asthma[16,17] and may contribute to all-cause mortality in patients with coronary artery disease.[18] Given the high prevalence of 25(OH)D deficiency and adverse outcomes in the general population, concern about whether this problem affects critically ill patients has arisen. In 2009, Lee and colleagues found that nearly 50% of patients admitted to intensive care units (ICUs) were 25(OH)D deficient, and this deficiency was associated with a 3-fold increase in mortality.[19] Since this report, several additional publications have linked 25(OH)D deficiency or insufficiency with increased severity of illness at ICU admission,[20] increased occurrence of acute kidney injury,[21] longer time to ICU discharge, greater risk of ICU-acquired infections,[22] fewer hospital-free days,[23] and increased all-cause mortality.[24]

Despite the association between 25(OH)D deficiency and adverse outcomes, whether vitamin D deficiency in critical illness contributes to poor outcomes or is a marker of severity of illness is not clear. Thus, equipoise remains regarding supplementation in the ICU and its effect on morbidity and mortality. To date, several randomized clinical trials (RCTs) have investigated various doses and durations of vitamin D_3 supplementation in critically ill patients.[25-30] Results have been quite mixed, with these studies including varying ICU populations (eg, surgical and medical) and using varying doses of vitamin D_3. Because we work in an institution in which vitamin D_3 supplementation during critical illness is relatively common, we performed an observational study both to improve our understanding of the associations of vitamin D_3 supplementation during medical critical illness with clinical outcomes (including ventilator-free days [VFDs] and hospital mortality) and to provide information on a more general medical ICU (MICU) population, rather than one recruited into clinical trials.

Methods/Statistics

In this single-center retrospective cohort study, we examined all patients admitted to the MICU service at the University of Vermont Medical Center (UVMMC) in Burlington, Vermont from January 1, 2009, to December 31, 2012. UVMMC is a tertiary referral hospital within a large catchment area that encompasses all of Vermont and much of northern New York, and our MICU team usually cares for approximately 150 patients annually who are mechanically ventilated for >3 days. Vitamin D (hereafter referred to as VITD) supplementation during critical illness at our institution is commonly suggested by our dietitians, with usual doses of 1000 international units (IU) daily, so we believed a priori that our sample of patients who received VITD over the study period would be reasonable. Using electronic health records, patients were included in our study if they were at least 18 years of age, mechanically ventilated for at least 72 hours, and cared for by the MICU clinical team (ie, excluded if cared for by surgery teams or another non-MICU team). We then grouped patients based on whether they received VITD at any time during the first 7 days of their MICU stay, as listed in their medication administration record. We chose this 7-day cutoff, as we expected VITD supplementation to have its greatest effect when delivered early, and the proportion of participants who did not receive VITD during the first week but then did receive it after day 7 was very small (<1%). Patients who were prescribed a multivitamin, but not VITD supplementation, during their hospitalization were not included in the VITD group for several reasons: (1) use of multivitamins in our ICU is relatively uncommon; (2) our hospital has several versions of multivitamins that range in VITD content from none to a usual maximum of 400 IU, thus the sample size of each individual dosing group would have been very small; and (3) even the maximum dose of VITD in the multivitamins was substantially lower than the 1000 IU that nearly all patients in our VITD group received (91.1%, see Results). Outcomes of interest were hospital mortality, VFDs, and ICU-free days (ICUFDs). VFDs and ICUFDs were defined, respectively, as the number of days during the first 28 days after MICU admission that the patient was alive and free from mechanical ventilation or alive and out of the MICU. Patients who died at any point during the

first 28 days were assigned 0 VFDs or ICUFDs. Covariates of interest selected a priori included: (1) Simplified Acute Physiology Score (SAPS) calculated from data recorded as close as possible to the time of admission; (2) age; (3) gender; (4) admission diagnosis based on *ICD-9* (*International Classification of Diseases, Ninth Revision*) codes; (5) race, categorized as Caucasian, black, or other; (6) admission day of the week (DOW; because we reasoned that patients admitted on Fridays or during a weekend might have VITD supplementation ordered later in their ICU course than patients admitted on other weekdays); (7) season of admission; and (8) VITD supplementation prior to ICU admission, which was determined by reviewing prior-to-admission medication lists. Patients who were taking any dose of VITD prior to admission were classified as taking outpatient VITD, and those listed as taking a multivitamin but not specific VITD supplementation were classified as not taking outpatient VITD. Unadjusted analyses were calculated using *t*-tests and χ^2 tests, with odds ratios (ORs) computed by using the Haldane-Anscombe correction when needed to adjust for cells with frequencies of 0. VFDs and ICUFDs were analyzed using linear regression, with VITD as the primary predictor, and including all of the covariates listed above. Hospital mortality was analyzed using logistic regression, with ORs, CIs, and their respective *P*-values calculated using bootstrap methodology because of the presence of cell frequencies of 0. Bootstrap estimates were based on 10,000 replications. All analyses were performed using SAS version 9.4 (Cary, NC, USA), and $P < 0.05$ was considered statistically significant. We also performed sensitivity analyses by analyzing potential outcome differences with patients grouped based on whether they received VITD specifically on day 1, day 3, or day 7, rather than at any time during their first 7 days, of their hospitalization. This study was approved by the University of Vermont Committee on Human Research in the Medical Sciences.

Results

A total of 2657 MICU patients were identified during the study time period, and 2047 were excluded because they received mechanical ventilation for <3 days, were under 18 years old, or were not cared for by the MICU team (eg, surgical patients). Of the 610 patients who met our inclusion criteria and were included in the analyses, 281 patients received VITD supplementation at any point during the first 7 days of their ICU stay, and 329 did not. Among the 281 patients receiving VITD, the median day of the first dose was ICU day 2 (interquartile range [IQR] day 1–3), and 91.1% were prescribed 1000 IU of VITD. As seen in Table 1, demographic and baseline characteristics including age, gender, race, SAPS, and DOW were not significantly different between the 2 groups. However, there were significant differences in season of admission, admission diagnosis, and whether patients were taking VITD prior to hospital admission. Compared with those who received VITD during their MICU admission, those who did not were more likely to be admitted during the winter and less likely during the spring, less likely to have a renal diagnosis at admission, and less likely to be taking VITD as an outpatient prior to hospitalization.

Table 1. Patient Characteristics at ICU Admission.

Characteristic	Received Vitamin D During ICU Stay (n = 281)	Did Not Receive Vitamin D During ICU Stay (n = 329)	*P*-Value
Age, years, mean ± SD	60.0 ± 15.0	59.6 ± 16.2	0.77
Gender, n (% men)	150 (53.4)	194 (59.0)	0.17
Race, n (%)			0.35
Caucasian	248 (88.3)	276 (83.9)	
Black	2 (0.7)	2 (0.6)	
Other, including >1 race	31 (11.0)	51 (15.5)	
Admission season, n (%)			0.04
Summer	51 (18.2)	66 (20.1)	
Fall	101 (35.9)	83 (25.2)	
Winter	74 (26.3)	105 (31.9)	
Spring	55 (19.6)	75 (22.8)	
Admission day of week, n (%)			0.88
Sunday	34 (12.1)	39 (11.8)	
Monday	41 (14.6)	44 (13.4)	
Tuesday	43 (15.3)	49 (14.9)	
Wednesday	42 (14.9)	44 (13.4)	
Thursday	44 (15.7)	51 (15.5)	
Friday	35 (12.5)	55 (16.7)	
Saturday	42 (14.9)	47 (14.3)	
SAPS score within first 24 hours of ICU admission, mean ± SD	34.4 ± 11.8	34.7 ± 11.4	0.7
Admission diagnoses, n (%)			0.02
Respiratory	105 (37.3)	124 (37.7)	
Cardiac	42 (14.9)	54 (16.4)	
Gastrointestinal	8 (2.9)	15 (4.6)	
Renal	23 (8.2)	8 (2.4)	
Neurologic	5 (1.8)	3 (0.9)	
Other	98 (34.9)	122 (37.1)	
>1 diagnosis	0 (0)	3 (0.9)	
Taking vitamin D prior to hospital admission, n (% yes)	54 (19.2)	37 (11.3)	0.006

ICU, intensive care unit; SAPS, sequential acute physiology score.

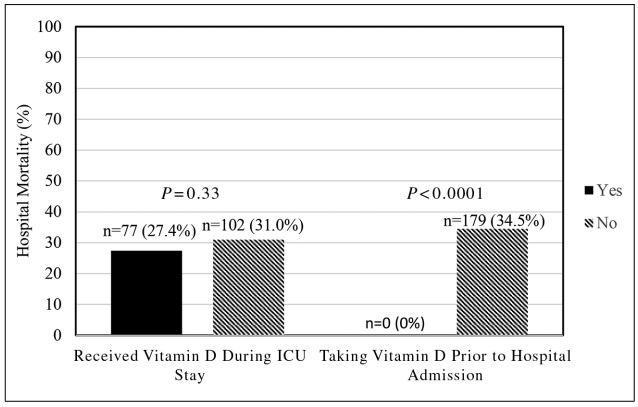

Figure 1. Unadjusted in-hospital mortality of patients who received and did not receive vitamin D during their intensive care unit (ICU) stay and patients who were and were not taking vitamin D prior to hospital admission.

Table 2. Unadjusted Ventilator-Free and ICU-Free Days by Patients Who Received and Did Not Receive Vitamin D During Their ICU Stay.

Outcome	Received Vitamin D During ICU Stay (n = 281)	Did Not Receive Vitamin D During ICU Stay (*n* = 329)	*P*-Value
Ventilator-free days, mean ± SD	14.2 ± 10.0	14.2 ± 10.6	0.99
ICU-free days, mean ± SD	12.8 ± 9.8	12.5 ± 10.0	0.69

ICU, intensive care unit.

As shown in Figure 1, of those patients who received VITD during their MICU admission, 27.4% died during hospitalization compared with 31% of patients who did not receive VITD (unadjusted OR = 0.84, 95% CI = 0.59–1.19, $P = 0.33$). Unadjusted in-hospital mortality was significantly different for patients who were taking VITD prior to admission (no patients died, 0%) vs those who were not (34.5%; OR = 0.01, 95% CI = 0.001–0.168, $P < 0.0001$).

As shown in Table 2, unadjusted VFDs for patients who received VITD during their ICU stay were 14.2 ± 10.0 vs 14.2 ± 10.6 for patients who did not ($P = 0.99$). Similarly, unadjusted ICUFDs for patients who received VITD were also not different compared with patients who did not receive VITD during their critical illness (12.8 ± 9.8 days and 12.5 ± 10.0 days, respectively, $P = 0.69$). When evaluating unadjusted VFDs and ICUFDs with participants grouped by those who were and were not taking VITD prior to hospital admission, significant results were demonstrated, as shown in Table 3. VFDs were significantly greater in patients who were taking VITD prior to admission (18.6 ± 7.3 days vs 13.5 ± 10.7 days, $P < 0.001$), as were ICUFDs (15.9 ± 7.9 days vs 12.1 ± 10.1 days, $P < 0.001$).

Table 3. Unadjusted Ventilator-Free and ICU-Free Days by Patients Who Were and Were Not Taking Vitamin D Prior to Hospital Admission.

Outcome	Were Taking Vitamin D Before Hospital Admission (n = 91)	Were Not Taking Vitamin D Before Hospital Admission (n = 519)	*P*-Value
Ventilator-free days, mean ± SD	18.6 ± 7.3	13.5 ± 10.7	<0.001
ICU-free days, mean ± SD	15.9 ± 7.9	12.1 ± 10.1	<0.001

ICU, intensive care unit.

Adjusted analyses revealed similar results as unadjusted analyses. After adjustment for age, gender, race, SAPS, admission season, DOW, and taking VITD prior to admission, neither in-hospital mortality, nor VFDs, nor ICUFDs were different between patients who received vs patients who did not receive VITD during their critical illness (Table 4). However, although receiving VITD during critical illness was not associated with differences in outcomes, adjusted analyses demonstrated that use of VITD prior to admission was associated with significantly more VFDs ($P = 0.04$) and ICUFDs ($P = 0.003$). These differences correspond to 21.0 ± 2.6 vs 17.6 ± 2.4 adjusted VFDs (mean ± standard error in days) and 18.5 ± 2.5 vs 16.3 ± 2.3 adjusted ICUFDs in those taking vs not taking VITD prior to admission. Adjusted analyses also demonstrated significantly increased survival in those taking VITD prior to admission (OR = 4.9×10^{-7}, 95% CI = 3.1×10^{-7} to 7.5×10^{-7}, $P < 0.0001$). These adjusted models additionally revealed that admission during the fall (compared with winter) and an increasing SAPS were associated with increased hospital mortality, and a decreasing SAPS was associated with more VFDs and ICUFDs (Table 4). Furthermore, having a gastrointestinal (GI) diagnosis at admission was associated with significantly more VFDs. GI diagnosis (most patients in this category had GI bleeding) was also associated with more ICUFDs, but this was not statistically significant ($P = 0.06$). Finally, increasing age was associated with increased odds of death.

The sensitivity analyses we performed by repeating the above analyses by grouping patients according to whether they received VITD on day 1, day 3, or day 7 of their MICU stay, rather than at any point during the first week of the ICU admission, produced similar results as above. In these sensitivity analyses, VITD supplementation while in the ICU was not associated with differences in clinical outcomes, but taking VITD prior to admission remained

Table 4. Adjusted Analyses for Ventilator-Free Days, ICU-Free Days, and Hospital Mortality.

	ICU-Free Days		Ventilator-Free Days		Mortality	
Outcome	β coefficient (95% CI)	*P*-value	β coefficient (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
Received vitamin D during ICU stay	0.26 (−1.24 to 1.77)	0.73	−0.14 (−1.71 to 1.44)	0.87	0.83 (0.52–1.31)	0.43
Taking vitamin D prior to hospital admission	**2.21 (0.10–4.32)**	**0.04**	**3.37 (1.15–5.58)**	**0.003**	**n = 0***	**<0.0001**
Age	−0.01 (−0.07 to 0.04)	0.64	−0.02 (−0.08 to 0.04)	0.46	**1.02 (1.00–1.04)**	**0.02**
Gender (men reference)	0.03 (−1.45 to 1.52)	0.97	−0.29 (–1.85 to 1.26)	0.71	1.15 (0.73–1.81)	0.53
Race						
Caucasian	0.36 (−1.76 to 2.48)	0.74	1.14 (−1.07 to 3.36)	0.31	0.88 (0.49–1.63)	0.68
Other	–ref–	–ref–	–ref–	–ref–	–ref–	–ref–
Admission season						
Summer	0.87 (−1.30 to 3.05)	0.43	0.41 (−1.86 to 2.68)	0.72	0.76 (0.38–1.51)	0.44
Winter	–ref–	–ref–	–ref–	–ref–	–ref–	–ref–
Fall	**−2.24 (−4.15 to 0.32)**	**0.02**	**−2.75 (−4.76 to 0.75)**	**0.007**	**2.26 (1.27–4.07)**	**0.006**
Spring	−1.38 (−3.47 to 0.71)	0.2	−1.41(−3.59 to 0.78)	0.21	1.44 (0.78 to 2.69)	0.24
Admission day of week						
Sunday	−0.22 (03.11–2.67)	0.88	−0.19 (−3.21 to 2.83)	0.9	1.35 (0.55–3.30)	0.52
Monday	−1.35 (−4.13 to 1.43)	0.34	−0.86 (−3.76 to 2.05)	0.56	1.16 (0.48–2.80)	0.74
Tuesday	0.52 (−2.23 to 3.27)	0.71	0.71 (−2.16 to 3.58)	0.63	0.77 (0.33–1.82)	0.54
Wednesday	–ref–	–ref–	–ref–	–ref–	–ref–	–ref–
Thursday	−1.90 (−4.60 to 0.79)	0.17	−1.34 (−4.16 to 1.48)	0.35	1.37 (0.63–3.04)	0.42
Friday	−0.70 (−3.45 to 2.05)	0.62	−0.50 (−3.37 to 2.37)	0.73	1.59 (0.71–3.59)	0.26
Saturday	−1.32 (−4.06 to 1.41)	0.34	−1.19 (−4.05 to 1.67)	0.41	1.60 (0.74–3.51)	0.23
SAPS Score	**−0.28 (−0.36 to 0.21)**	**<0.0001**	**−0.30 (−0.37 to 0.22)**	**<0.0001**	**1.08 (1.05–1.11)**	**<0.0001**
Admission diagnoses						
Respiratory	0.72 (−0.98 to 2.43)	0.41	0.55 (−1.24 to 2.33)	0.55	0.93 (0.57–1.51)	0.78
Cardiac	−1.13 (−3.37 to 1.11)	0.32	−1.20 (−3.54 to 1.14)	0.31	1.34 (0.67–2.59)	0.39
Gastrointestinal	**3.88 (0.12–7.65)**	**0.04**	3.84 (−0.09 to 7.77)	0.06	0.14 (0.07–1.20)	0.52
Renal	0.56 (−2.97 to 4.08)	0.76	0.31 (−3.38 to 3.99)	0.87	1.16 (0.41–3.21)	0.77
Neurologic	4.69 (−1.86 to 11.23)	0.16	5.50 (−1.35 to 12.35)	0.12	**n = 0****	**<0.0001**

Ref, indicates reference group in multivariable models.
Significantly different results ($p<0.05$) are in bold font.
ICU, intensive care unit; SAPS, sequential acute physiology score.
*Odds ratio for vitamin D taken prior to admission: 4.9×10^{-7}, 95% CI = 3.1×10^{-7} to 7.5×10^{-7}.
**Odds ratio for neurology admission diagnosis: 1.0×10^{-6}, 95% CI = 2.3×10^{-7} to 5.7×10^{-6}.

significantly associated with more VFDs, more ICUFDs, and greater hospital survival (data not shown).

Discussion

Our results demonstrate that there is no association of VFDs, ICUFDS, or mortality with receiving VITD during the first week of critical illness, with either adjusted or unadjusted analyses. Very interestingly, we did find significant and compelling associations between taking VITD prior to hospitalization and improved mortality, more VFDs, and more ICUFDs—both with unadjusted and adjusted analyses.

Our results of VITD supplementation in the ICU are consistent with 2 recent meta-analyses that found no improvement in survival, ICU length of stay, or duration of mechanical ventilation, including whether VITD was delivered orally or parenterally or in a high dose.[31,32] The 3 largest randomized trials to date also found similar results overall.[26,27,29] These results, in total, would suggest that VITD supplementation during critical illness may not improve outcomes, although the largest prior RCT of high-dose VITD supplementation in critically ill patients did find an improvement in survival among the subgroup with severe VITD deficiency.[27] An ongoing large clinical trial of high-dose VITD supplementation early in critical illness will help to answer this question (NCT03096314).

Explanations for our findings of significantly improved outcomes being so strongly associated with taking VITD prior to hospitalization are perhaps less clear. It may be that

those patients who were not taking VITD supplements prior to admission were truly deficient in 25(OH)D which would be consistent with previous retrospective studies that found deficiency was associated with adverse outcomes.[18,33,34] Given the important impact of VITD on innate and adaptive immunity as described above, it is certainly biologically plausible that consistent VITD supplementation prior to critical illness might alter outcomes. Another explanation includes residual confounding; in other words, perhaps those patients who take VITD supplements as outpatients have some unmeasured and unknown factor that is associated with a survival advantage and with improved clinical outcomes after critical illness. Patients who were taking VITD at the time of hospital admission did have a significantly lower SAPS than those who were not (30.4 ± 10.3 vs 35.2 ± 11.7, $P = 0.0002$), but even after adjustment for severity of illness in our models, taking VITD before admission remained a very strong predictor of outcome. Nonetheless, there may be additional factors not included in severity of illness measures such as SAPS that might confound the relationship between VITD and outcome. It is also possible that patients who were taking VITD prior to admission may have had more consistent and established primary care, perhaps resulting in an increased likelihood of measuring plasma VITD levels and receiving VITD supplementation if found to be deficient. Better primary care prior to hospitalization could also have resulted in a survival advantage in these patients. An additional explanation is that our results are incorrect (ie, similar to a type I error), but the association we found is so strong that additional research into this issue is warranted.

There are several limitations to this study. First, as this was a retrospective study using electronic medical record data, 25(OH)D levels were not measured in this cohort prior to VITD administration. However, the age, ethnicity, and latitude of our patient population is very similar to a 2012 study of 1325 patients from 2 teaching hospitals in Boston, Massachusetts, in which 86.0% of participants had 25(OH)D levels <30 ng/mL (ie, deficient).[24] Therefore, we can safely assume that a majority of patients in our cohort were also VITD deficient at the time of their critical illness, but we do not have confirmatory levels. Additionally, even if levels were available in our study, controversy remains regarding the definition of deficiency. The Institute of Medicine has concluded that a serum 25(OH)D concentration of 20 ng/mL is sufficient,[35] whereas the Endocrine Society recommends a minimum 25(OH)D level above 30 ng/mL, which relatively few individuals in the United States achieve.[36] Second, although our sample size is relatively large, this study is single center and therefore may lack generalizability. Our results may not translate to other ICU populations in different locations. Third, supplementation of VITD at our hospital often results from dietitian recommendations. As we do not have an institutional guideline about VITD supplementation during hospitalization, these recommendations are made on a case-by-case basis. Although we adjusted for potential confounding factors that might affect whether patients receive VITD in the hospital (Table 1), selection bias could have occurred and might affect our results in unknown ways. For example, it is important to note that patients who received VITD in the ICU were more likely to have been taking VITD prior to hospital admission (19.2%) than those who did not receive VITD while critically ill (11.3%). Although we adjusted for prior-to-admission VITD, there could be other factors that led to the decision to prescribe VITD in the ICU that are unknown. Fourth, misclassification of 1 or more variables in our retrospective study may have affected our results. For example, we cannot be certain who was and was not taking VITD prior to admission, as the information we used were pharmacy records. Finally, we were not able to ascertain the degree of primary care prior to hospitalization because a large fraction of our hospitalized patients do not receive primary care within our health network system. Thus, the results of this study are meant to be exploratory.

Despite their limitations, our results indicate a strong association between VITD supplementation prior to hospital admission and improved outcomes among critically ill, mechanically ventilated adults. It may be that VITD supplementation after critical illness has begun indeed does not affect outcomes, because the opportunity for supplementation to have beneficial effects has already passed, but that supplementation before acute severe illness may improve outcomes in those who become critically ill. These results should prompt additional research on this question at other centers and in other populations to determine whether widespread VITD supplementation in ambulatory patients at high risk of critical illness may be warranted.

Statement of Authorship

T. R. Leclair and R. D. Stapleton equally contributed to the conception and design of the research; N. Zakai contributed to the design of the research and acquisition of data; J. Y. Bunn contributed to the design of the research and analyses of the data; M. Gianni and S. S. Ardren contributed to the acquisition of the data; D. K. Heyland contributed to the design of the research and interpretation of the data; and T. R. Leclair, R. D. Stapleton, and J. Y. Bunn drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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