Neither vitamin D levels nor supplementation are associated with the development of persistent critical illness: a retrospective cohort analysis

Elizabeth M Viglianti,* Paul Zajic,* Theodore J Iwashyna and Karin Amrein

Vitamin D deficiency is associated with disease severity, sepsis, increased intensive care and hospital length of stay, and mortality.[1-3] Furthermore, vitamin D deficiency has been hypothesised to worsen critical illness through its mediating effects on the immune, cardiac and vascular systems.[4] It can be identified either before or very early in a hospitalisation, making it a readily accessible biomarker to use and intervene upon in critically ill people.

A recent study, the VITdAL-ICU randomised clinical trial of vitamin D supplementation in critically ill patients (ClinicalTrials.gov identifier: NCT01130181), reported a mortality benefit in a subgroup analysis of patients with severe vitamin D deficiency (defined as ≤ 12 ng/mL), but it did not find an overall mortality benefit or reduced hospital length of stay in the primary analysis of all patients with 25-hydroxyvitamin D (25(HO)D) levels < 20 ng/mL.[5] These findings have prompted two ongoing large randomised controlled trials to evaluate the role of vitamin D: Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET) in patients at risk for acute respiratory distress syndrome (NCT03096314), and Effect of High-dose Vitamin D_3 on 28-day Mortality in Adult Critically Ill Patients with severe vitamin D deficiency (VITDALIZE) (NCT03188796).

In light of the associations of vitamin D deficiency and critical care outcomes, it seems plausible that vitamin D may play a causal role in the development of persistent critical illness. This is particularly true since a major event for many patients with persistent critical illness has been argued to be the development of late septic shock, for which vitamin D deficiency's negative impact on immune and cardiovascular function may contribute.[1,4,6] Given vitamin D's protean effects, we sought to generate hypotheses regarding:

- patients with vitamin D deficiency are more likely to develop persistent critical illness (hypothesis 1); and
- the development of persistent critical illness will be mitigated by vitamin D_3 supplementation (hypothesis 2).

Therefore, we conducted a secondary re-analysis of the de-identified data from a retrospective cohort study conducted at the University Medical Center of Graz in 2014 and the VITdAL-ICU randomised controlled trial in order to test these hypotheses.[5,7]

ABSTRACT

Objective: The purpose of this study was to evaluate if vitamin D deficiency is associated with increased rates of persistent critical illness, and whether repletion of vitamin D among patients with this deficiency leads to decreased persistent critical illness.

Design: Retrospective cohort analysis.

Setting: Seven intensive care units (ICUs) at the University Medical Center of Graz, Austria, with participants recruited between July 2008 and April 2010. The VITdAL-ICU trial cohort included five ICUs at the University Medical Center of Graz, Austria, with patients recruited between May 2010 through September 2012.

Participants: There were 628 patients aged ≥ 18 years admitted to the ICU and who had their 25-hydroxyvitamin D (25(OH)D) level measured at least once. The VITdAL-ICU cohort included 475 patients aged ≥ 18 years who were expected to stay in the ICU for greater than 48 hours and found to have a 25(OH)D level of ≤ 20 ng/mL.

Main outcome measures: Development of persistent critical illness.

Results: In the retrospective cohort, vitamin D level on admission was not significantly associated with the development of persistent critical illness compared with patients who were discharged alive earlier (relative risk ratio [RRR], 1.02; 95% CI, 1.00–1.04) or who died (RRR, 1.02; 95% CI, 0.99–1.05). In the VITdAL-ICU trial, supplementation with vitamin D_3 did not lead to less persistent illness relative to patients who were discharged alive earlier (RRR, 1.19; 95% CI, 0.79–1.80) or who died (RRR, 1.34; 95% CI, 0.72–2.52).

Conclusion: Vitamin D deficiency was not associated with persistent critical illness, nor did supplementation with vitamin D_3 mitigate the development of persistent critical illness.

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Methods

We conducted a retrospective study in a university hospital from a cohort of patients admitted to the ICU from July 2008 to April 2010 and from May 2010 to September 2012. As these were secondary analyses of de-identified data, they were exempt from human subjects review.

The University Medical Center of Graz is a large tertiary academic centre in the southeast of Austria with 1538 beds, including 123 ICU beds.

Study populations

The initial retrospective cohort study was conducted in all adult patients treated in one of seven medical, neurological, neurosurgical, cardiothoracic and mixed surgical–medical ICUs at the University Medical Center of Graz, Austria, between July 2008 and April 2010 who had their 25(OH)D level measured at least once.[7] Screening for vitamin D deficiency was performed on request of the treatment team in this time period. The median time in the ICU until the 25(OH)D level was drawn was 2 days (interquartile range [IQR], 1–4). 25(OH)D levels and other routine data gathered during hospital stay were extracted from the hospital's medical documentation system and analysed in 2014.

The VITdAL cohort has been previously described in detail.[5,8] The patients were recruited from five ICUs: medical, neurological, cardiothoracic surgery and two mixed surgical–medical units. Patients aged ≥ 18 years, who were expected to stay in the ICU for greater than 48 hours and were found to have a 25(OH)D level ≤ 20 ng/mL were eligible to participate in the study. Patients were excluded from the trial if they met any of the following criteria:

- severely impaired gastrointestinal function;
- other trial participation;
- pregnant or lactating women;
- hypercalcaemia (total calcium > 10.6 mg per day);
- tuberculosis, sarcoidosis, nephrolithiasis within the prior year; and
- patients deemed not suitable.

Patients were randomly assigned to either a placebo group or a vitamin D_3 group in a 1:1 ratio. Patients randomly allocated to the vitamin D_3 group received a loading dose of 540 000 IU of vitamin D_3.

Key definitions

Vitamin D deficiency and severe vitamin D deficiency were defined as ≤ 20 ng/mL and < 12 ng/mL, respectively. The patient's screening 25(OH)D level was used for the analysis.

Persistent critical illness was defined as ICU stay of ≥ 10 days based on population-based data.[9,10]

Analysis

We present patient characteristics as counts (percentages), means (standard deviation [SD]), or medians (IQR) as appropriate. Charlson comorbidities were tabulated using the method of Deyo.[11,12] We conducted all analysis with Stata software version 15.1 (StataCorp, College Station, TX).

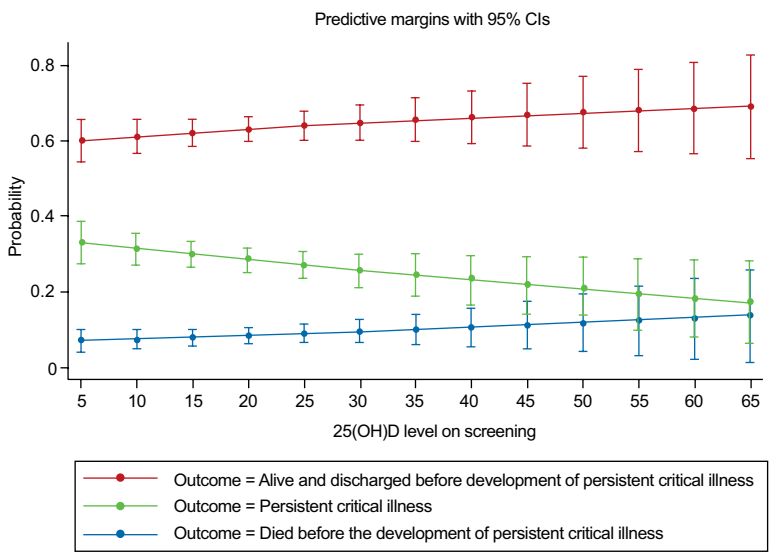
Multinomial logistic regression identified patient characteristics on ICU admission associated with the development of persistent critical illness. Covariates were chosen a priori.

Results

Retrospective cohort results

In the retrospective cohort of 655 patients, 628 were included in the analysis. Patients were excluded if data were missing. Of the 628 patients, 37.4% (n = 235) were female, with a median age of 65 years (IQR, 52–75). The mean Simplified Acute Physiology Score (SAPS) II score and the mean Therapeutic Intervention Scoring System-28 (TISS-28) score on admission were 29.4 (SD, 15.7) and 31.7 (SD, 8.8), respectively. The mean 25(OH)D level was 17.4 ng/mL (IQR, 11.2–25.2). The hospital and ICU mortality rates were 18.5% and 13.2%, respectively (Table 1).

Figure 1. Margins plot of the adjusted association of vitamin D levels and intensive care unit outcomes, from logistic regression of the retrospective cohort*



25(OH)D = 25-hydroxyvitamin D. * The slope of the line for the development of persistent critical illness was not statistically significantly different from zero.

Table 1. Patient demographics in the retrospective cohort and the VITdAL-ICU trial cohort

Patient baseline characteristics	Retrospective cohort	VITdAL ICU cohort (*n* = 475)	
	n = 628	Placebo (*n* = 238)	Vitamin D_3 (*n* = 237)
Gender, female	235 (37.4%)	83 (34.9%)	83 (35%)
Age (years), median (IQR)	65 (52–74.5)	68 (56–76)	66 (55–75)
SAPS II at ICU admission, mean (SD)	29.4 (15.7)	34.2 (15.7)	32.4 (15)
TISS-28, mean (SD)	31.7 (8.8)	38.0 (8.2)	37.7 (7.6)
25-Hydroxyvitamin D (ng/mL), mean (SD)	19.6 (11.3)	13.1 (4.3)	13.0 (4.0)
ICU mortality	83 (13.2%)	63 (26.5%)	54 (22.8%)
Hospital mortality	116 (18.5%)	84 (35.3%)	67 (28.3%)
ICU LOS (days), median (IQR)	6 (3–11)	10.7 (0.1–154.1)	9.6 (0.2–181)
Persistent critical illness	181 (28.8%)	116 (48.7%)	106 (44.7%)
Hospital LOS (days), median (IQR)	7 (0–15)	19.3 (0.1–154.1)	20.1 (0.2–181)
ICU type			
Cardiac surgery	102 (16.2%)	69 (29%)	68 (28.7%)
Medical	228 (36.3%)	53 (22.3%)	52 (21.9%)
Mixed surgical–medical	110 (17.5%)	58 (24.4%)	59 (24.9%)
Neurological	160 (25.5%)	61 (25.6%)	54 (22.8%)
Neurosurgery	28 (4.5%)	na	na

ICU = intensive care unit. IQR = interquartile range. LOS = length of stay. na = not applicable. SAPS = Simplified Acute Physiology Score. SD = standard deviation. TISS-28 = Therapeutic Intervention Scoring System-28.

Among the retrospective cohort patients, lower TISS-28 scores and being admitted to a neurosurgical ICU were associated with patients not developing persistent critical illness and remaining alive. Vitamin D_3 level on admission was not significantly associated with the development of persistent critical illness compared with patients discharged alive earlier or who died before the onset of persistent critical illness (Table 2 and Figure 1). Across the entire observed range, the probability of developing persistent critical illness fell from about 30% among patients with 25(OH)D levels < 20 ng/mL to about 20% among patients with 25(OH)D levels > 50 ng/mL, but these apparent differences were not statistically significant or robust across multiple non-linear specifications of the vitamin D measurements. Vitamin D was also not associated with the development of persistent critical illness compared with patients who did not develop persistent critical illness (binary outcome variable; odds ratio [OR], 0.98; 95% CI, 0.96–1.00). When dichotomising vitamin D level ≤ 12 ng/mL, there was also no statistically significant association with the development of persistent critical illness compared with patients discharged alive earlier or patients who died before the onset of persistent critical illness in adjusted multinomial logistic regression; or compared with patients who did not develop persistent critical illness in adjusted binary logistic regression. This result refutes hypothesis 1.

VITdAL study secondary analysis

In the VITdAL-ICU study, 475 patients participated and were included in our analysis. Of the 475 patients, 238 were assigned to the placebo group and 237 were allocated to the treatment group; 98% and 96% of each arm received the intervention as randomised. In the placebo and treatment groups, 34.9% of participants (*n* = 83) were female. The median age was 68 years (IQR, 56–76) and 64 years (IQR, 56–76), respectively. The mean 25(OH)D level was 13.1 ng/mL (SD, 4.3) in the placebo group and 13.0 ng/mL (SD, 4.0) in the treatment group (Table 1).

Among patients with vitamin D deficiency, regardless of whether the patient was randomly assigned to the treatment or the placebo group, it did not distinguish between those patients who would be discharged alive before the onset of persistent critical illness (relative risk ratio [RRR], 1.19; patients who were discharged alive before the development of persistent critical illness *v* patients who developed persistent critical illness; 95% CI, 0.79–1.80) or who died before the onset of persistent critical illness (RRR, 1.34; patients who died before the onset of persistent critical illness *v* patients who developed persistent critical illness; 95% CI, 0.72–2.52) in intention-to-treat analyses (Table 3). Group assignment was also not associated with the development of persistent critical illness, measured as a dichotomous variable (OR, 0.84; 95% CI, 0.57–1.23). Among patients with vitamin D_3 levels ≤ 12 ng/mL, there was also no association between randomisation to treatment versus placebo with the development of persistent critical illness compared with patients who were discharged alive earlier (RRR, 0.92; 95% CI, 0.61–1.40) or who died (RRR, 1.62; 95% CI, 0.85–3.08) in an intention-to-treat analysis. This result refutes hypothesis 2.

Table 2. Logistic regression for the retrospective cohort compared with patients who developed persistent critical illness*

	Alive and discharged before persistent critical illness		Dead before onset of persistent critical illness	
	RRR	95% CI	RRR	95% CI
25-Hydroxyvitamin D (per ng/mL)	1.02	1.00–1.04	1.02	0.99–1.05
SAPS II (per point)	0.99	0.97–1.00	0.99	0.97–1.01
TISS-28 (per point)	0.89	0.87–0.92	1.01	0.98–1.06
Age (per year)	1.01	1.00–1.03	1.04	1.01–1.06
ICU type				
Medical	0.84	0.48–1.47	0.84	1.11–9.18
Mixed surgical–medical	1.04	0.55–1.98	2.10	0.64–8.71
Neurological	1.03	0.52–2.03	2.39	0.07–8.71
Neurosurgery	0.07	0.02–0.21	0.37	0.04–3.50

ICU = intensive care unit. RRR = relative risk ratio. SAPS = Simplified Acute Physiology Score. TISS-28 = Therapeutic Intervention Scoring System-28.
* The comparison group included those patients who developed persistent critical illness.

Table 3. Logistic regression for the VITdAL-ICU trial cohort compared with patients who developed persistent critical illness*

	Alive and discharged before persistent critical illness		Dead before onset of persistent critical illness	
	RRR	95% CI	RRR	95% CI
25-Hydroxyvitamin D (per ng/mL)	1.03	0.98–1.08	0.96	0.89–1.04
Age (per year)	1.01	1.00–1.03	1.03	1.01–1.06
SAPS II (per point)	1.00	0.99–1.01	1.01	0.99–1.02
Charlson Comorbidity Index (per point)	0.93	0.84–1.04	1.02	0.88–1.18
TISS-28 (per point)	0.92	0.89–0.95	1.09	1.03–1.14
Treatment				
Yes (*v* placebo)	1.19	0.79–1.80	1.34	0.72–2.52
ICU type (*v* medical ICU)				
Neurological	1.02	0.53–1.99	0.53	0.20–1.43
Cardiosurgical	0.73	0.40–1.32	0.14	0.06–0.33
Mixed surgical–medical	0.53	0.28–0.99	0.17	0.07–0.41

ICU = intensive care unit. RRR = relative risk ratio. SAPS = Simplified Acute Physiology Score. TISS-28 = Therapeutic Intervention Scoring System-28.
* The comparison group included those patients who developed persistent critical illness.

Discussion

Key findings

Despite plausible physiological rationale, vitamin D deficiency was not associated with the development of persistent critical illness in a secondary analysis of a cohort study. In a secondary analysis of a randomised clinical trial, supplementation with vitamin D_3 in critically ill patients with vitamin D deficiency did not mitigate the development of persistent critical illness. In both cases, the best estimate effect was itself quite close to the null, suggesting that this lack of association is a truly negative finding and not solely due to a lack of power in the study design.

Relationship to previous studies

Vitamin D deficiency is associated with sepsis, prolonged ICU stay, acute kidney injury and mortality.[1,4,13,14] Whether supplementation would help mitigate the development or severity of these organ failures has remained unclear. The VITdAL-ICU trial was the first large randomised controlled trial to explore vitamin D supplementation in critically ill patients, and although it reported no difference in the primary outcome — hospital length of stay — it was suggestive of a mortality benefit in patients with severe vitamin D deficiency (vitamin D level ≤ 12 ng/mL).[5] The role of vitamin D deficiency in persistent critical illness was unknown.

Patients with persistent critical illness have prolonged ICU stays.[10,15,16] Their ICU courses can be defined by dynamic cascading late organ failure or non-resolving single organ failure. Recently, patients with persistent critical illness were described as predominately developing dynamic cascading organ failures, which was principally late cardiovascular failure and, specifically, septic shock.[6] In light of the known relationship between vitamin D deficiency and sepsis, it would seem plausible that vitamin D_3 supplementation could mitigate the development of late septic shock in patients with persistent critical illness. Furthermore, given the dynamic cascade of organ failures described in persistent critical illness, and the association of vitamin D with other organ failures — acute renal failure and acute respiratory distress syndrome — vitamin D_3 supplementation may have helped to mitigate these additional organ failures.[13]

Strength and limitations

Our study is a secondary analysis and, like any secondary data analysis, it is susceptible to the risks criticised as "*P*-hacking". In order to minimise the risks of *P*-hacking in our study, we have been explicit that our examinations were intended to develop hypotheses, not provide a definitive test of them. Second, both cohorts were from a single centre in Austria, which may limit the generalisability of the findings to other centres and patient cohorts. However, the cohorts did entail a diverse clinical population from different ICUs. Third, in the VITdAL-ICU trial, despite supplementation, not all participants in the trial arm reached 25(OH)D levels ≥ 30 ng/mL by Day 3 and Day 7 in the ICU.

Conclusion

Vitamin D deficiency is not associated with the development of persistent critical illness and supplementation did not mitigate the development of persistent critical illness in this secondary analysis of an existing cohort study and randomised clinical trial. This suggests that pre-existing vitamin D levels are not a major driver of persistent critical illness and prolonged ICU stay, which is consistent with the argument that a major driver of persistent critical illness is in-ICU events and intercurrent problems, rather than conditions present on admission.

Competing interests

None declared.

Author details

Elizabeth M Viglianti*[1]

Paul Zajic*[2]

Theodore J Iwashyna[1,3,4]

Karin Amrein[2]

*** Equal first authors.**

1 Department of Internal Medicine, Division of Pulmonary and Critical Care, University of Michigan, Ann Arbor, MI, USA.

2 Department of Anesthesiology and Intensive Care Medicine, Division of General Anesthesiology, Emergency and Intensive Care Medicine, Medical University of Graz, Graz, Austria.

3 Veterans Affairs Center for Clinical Management Research, VA Ann Arbor Healthcare System, Ann Arbor, MI, USA.

4 Institute for Social Research, University of Michigan, Ann Arbor, MI, USA.

5 Department of Internal Medicine, Division of Endocrinology and Diabetology, Medical University of Graz, Graz, Austria.

***Correspondence*:** eviglian@med.umich.edu

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Disclaimer

This work does not represent the official views of the United States Government or of the Department of Veterans Affairs.

Study site

The analysis was performed at the University of Michigan in the Department of Internal Medicine, Division of Pulmonary Critical Care.

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