The Association of Serum Vitamin D Concentration with Serious Complications After Noncardiac Surgery

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BACKGROUND: Vitamin D deficiency is a global health problem. Epidemiological studies demonstrate that vitamin D is both cardioprotective and neuroprotective. Vitamin D also plays a substantial role in innate and acquired immunity. Our goal was to evaluate the association of serum vitamin D concentration on serious postoperative complications and death in noncardiac surgical patients.

METHODS: We retrospectively analyzed the data of 3509 patients who had noncardiac surgery at the Cleveland Clinic Main Campus and had a serum vitamin D measurement. The relationship between serum vitamin D concentration and all-cause in-hospital mortality, in-hospital cardiovascular morbidity, and serious in-hospital infections was assessed as a common effect odds ratio (OR) by using a multivariate generalized estimating equation model with adjustment for demographic, medical history variables, and type and duration of surgery.

RESULTS: Higher vitamin D concentrations were associated with decreased odds of in-hospital mortality/morbidity (P = 0.003). There was a linear reduction of the corresponding common effect odds ratio (OR 0.93, 95% confidence interval, 0.88–0.97) for severe in-hospital outcomes for each 5 ng/mL increase in vitamin D concentration over the range from 4 to 44 ng/mL. In addition, we found that the odds versus patients with vitamin D <13 ng/mL (i.e., 1st quintile) were significantly lower in patients with vitamin D 13–20, 20–27, 27–36, and > 36 ng/mL (i.e., 2nd–5th quintiles); the corresponding estimated ORs were 0.65 (99% confidence interval, 0.43–0.98), 0.53 (0.35–0.80), 0.44 (0.28–0.70), and 0.49 (0.31–0.78), respectively. However, there was no statistically significant difference among individual quintiles >13 ng/mL.

CONCLUSIONS: Vitamin D concentrations were associated with a composite of in-hospital death, serious infections, and serious cardiovascular events in patients recovering from noncardiac surgery. While causality cannot be determined from our retrospective analysis, the association suggests that a large randomized trial of preoperative vitamin D supplementation and postoperative outcomes is warranted. (Anesth Analg 2014;119:603–12)

Vitamin D (25-hydroxyvitamin D) deficiency (<25 nmol/L or <10 ng/mL) or insufficiency (25–75 nmol/L or 10–30 ng/mL)[1] affects >1 billion people worldwide, spanning age groups, ethnicities, and gender.[2] In the United States, more than one-third of adults,[3,4] more than half of all hospitalized patients,[5] and >95% of critically ill patients have a vitamin D deficiency.[6]

The multifaceted implications of vitamin D deficiency have long been recognized. For example, in a discussion on rickets at the Annual Meeting of the British Medical Association in 1888, WB Cheadle stated, "…the first point upon which I would venture to insist is that rickets is not to be regarded as a mere affection of the bones …. but it is something far more than this; the disease affects not only bones but muscles and ligaments, mucous membrane and skin, the blood and the nervous system."[7]

There is now better understanding of the ways vitamin D contributes to vital processes aside from its "traditional" role in skeletal maintenance. Vitamin D receptors are found in most of the immune system cells, including macrophages, B and T lymphocytes, and neutrophils.[8] Vitamin D also regulates antimicrobial peptide gene expression, thus improving innate immunity.[6,9,10] As might therefore be expected, vitamin D deficiency is associated with infections, particularly respiratory infections.[9,11,12]

Low vitamin D concentrations are also associated with inflammation, especially in patients with cardiac disease.[13] Inflammation increases the risk of cardiovascular disease and accompanies about 80% of all sudden cardiac deaths.[14,15] It is thus not surprising that multiple investigations support a link between vitamin D deficiency and cardiovascular risk.[16–18]

The summative effects of vitamin D were evaluated in a prospective cohort from the Third National Health and Nutrition Examination Survey (NHANES III), a program designed to assess the health and nutritional status in the United States by combining interviews and physical examinations. NHANES III demonstrated an association between vitamin D deficiency and all-cause mortality.[4,19]

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Accepted for publication November 26, 2013.

Funding: Support was provided solely from institutional and/or departmental sources. None of the authors has a personal financial interest in this research.

The authors declare no conflicts of interest.

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DOI: 10.1213/ANE.0000000000000096

Postsurgical patients are particularly susceptible to cardiovascular and infectious complications, both of which appear to be aggravated by vitamin D deficiency, which itself is common in surgical patients. Compelling evidence thus suggests that patients with vitamin D deficiency may have worse outcomes than those with optimal concentrations, but this has not previously been studied in surgical patients. We therefore tested the primary hypothesis that noncardiac surgical patients with lower perioperative serum vitamin D concentrations are more likely to experience a composite outcome of all-cause in-hospital mortality, in-hospital cardiovascular morbidity, and in-hospital infectious morbidity.

METHODS

With IRB approval, written informed consent was waived for this retrospective cohort analysis of 3509 adult patients. Analysis was restricted to patients who had noncardiac surgery at the Cleveland Clinic Main Campus between 2005 and 2011 and had at least one 25-hydroxyvitamin D measurement in the period starting 3 months before the procedure date to 1 month after, at our institution's laboratory. We excluded pediatric patients and patients with ASA physical status >4.

Vitamin D concentrations were obtained from the Laboratory Medicine registry. Other data were obtained from the Cleveland Clinic Perioperative Health Documentation System, a registry in which data are prospectively collected.

The aim of the study was to evaluate the relationship between serum vitamin D concentration and all-cause in-hospital mortality, in-hospital cardiovascular morbidity, and serious in-hospital infections (definitions in Appendix 1). We did not analyze the 3 outcomes as a collapsed composite ("any-versus-none") or analyze them separately. Rather, we assessed the "common effect" or "global" odds ratio (OR) of serum vitamin D concentration across the above 3 in-hospital outcomes, by using a multivariate (i.e., multiple outcomes) generalized estimating equation (GEE) model with unstructured covariance matrix to simultaneously capture the complete information on each outcome for a patient and to adjust for the within-patient correlation among the outcomes.[20] The model was fit with adjustment for potential confounding variables listed in the Table 1 including the demographic, medical history variables, and type and duration of surgery. We assumed linear relationship between logit of the probability of having outcome and the continuous independent variables. To visualize the association of the composite outcome and the vitamin D concentration, we plotted the estimated probability (on the logit scale) of having in-hospital mortality/morbidity as a function of vitamin D concentration by using a multivariate GEE model incorporating a smooth term for vitamin D concentration. In addition, we also plotted the common effect OR (99% confidence interval [CI]) of each quintile of vitamin D concentration compared with the lowest quintile.

We assessed the heterogeneity of the vitamin D effect across the components of the in-hospital outcomes by testing the vitamin D-by-outcome interaction in a separate "distinct-effect" GEE model, which enables adjustment for the correlation among the component outcomes.[20] The heterogeneity test compares the OR (log scale) for vitamin D concentration among the individual outcomes of interest. Significant heterogeneity, especially in opposite directions, would suggest that the individual ORs be given more importance than the global OR.[21,22] Although the associations proved to be homogeneous among the individual outcomes (vitamin D-by-outcome interaction, $P = 0.73$), we nonetheless report associations between perioperative vitamin D concentration and specific in-hospital outcomes by using a GEE model, adjusting for the same potential confounders. A Bonferroni correction was used to adjust for testing multiple outcomes; thus, 98.3% CI were reported, and the significance criterion for the 3 primary outcomes was $P < 0.017$ (i.e., 0.05/3).

Hypotensive episodes may be due to vasopressor resistance in patients with lower vitamin D concentrations. We descriptively displayed the relationship between vitamin D concentration and intraoperative hemodynamic characteristics, including heart rate, arterial blood pressure, transfusions, and use of vasopressors (dobutamine, dopamine, epinephrine, norepinephrine, phenylephrine, and vasopressin) by reporting the summary statistics for each quintile of vitamin D concentration. Intraoperative hemodynamic data were acquired from our electronic anesthesia record-keeping system, which continuously records minute-by-minute data from physiologic monitors throughout anesthesia. Arterial blood pressure in patients with arterial catheters was recorded each minute; otherwise, pressure was measured oscillometrically and recorded at 1- to 5-minute intervals.

Sample Size Considerations

Available power for the study was assessed post hoc by comparing low versus normal concentrations of vitamin D (<25 ng/mL and ≥25 ng/mL) on the set of in-hospital outcomes by using a SAS macro developed for designs with multiple binary correlated end points ("multibinpow") by using 1000 simulations.[a] With 3500 patients (1750/group), we had >90% power at the 0.05 significance level to detect a common effect OR of 0.7 or stronger for patients with vitamin D ≥25 ng/mL vs <25 ng/mL, by using the observed incidences of 1.65% for mortality, 6.69% for cardiovascular morbidity, and 8.82% for infectious morbidity (patients with vitamin D <25 ng/mL), and assuming a compound symmetric correlation structure with a between-outcome correlation of 0.05. Our study is more highly powered because vitamin D levels were analyzed as a continuous exposure variable.

SAS version 9.3 (SAS Institute, Cary) and R version 2.12.0 (The R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses.

RESULTS

Vitamin D levels were measured in 3509 patients; the median 25-hydroxyvitamin D concentration was 23.5 [1st–3rd quartiles: 14.6–33.6] ng/mL. The median [1st–3rd quartiles] difference between the vitamin D observation

[a]Mascha EJ. Power Calculations for Tests on a Vector of Binary Outcomes (MULTBINPOW). Cleveland Clinic Statistical Software Series 10 edn 2011. Available at: http://www.lerner.ccf.org/qhs/software/multbinpow.php

Table 1. Demographics and Baseline Medical Conditions for 3509 Noncardiac Surgical Patients by Quintiles of Serum Vitamin D Concentration

	Serum vitamin D concentration (ng/mL)					
Variable	≤ 13, (*N* = 702)	13.1–20.4, (*N* = 709)	20.5–27.3, (*N* = 711)	27.4–36.2, (*N* = 692)	>36.2 (*N* = 695)	*P**
Age, y	55 ± 15	57 ± 15	59 ± 15	60 ± 15	61 ± 15	<0.001†
Gender (male), %	47	44	38	37	32	<0.001
Race, %						<0.001
Caucasian	61	73	79	81	82	
African American	33	20	16	15	14	
Others	6	6	5	4	5	
Body mass index, kg/m^2	28 [24–34]	28 [24–34]	28 [24–33]	28 [24–33]	27 [23–31]	<0.001‡
ASA physical status, %						<0.001
I	1	1	1	1	1	
II	14	24	27	31	33	
III	58	60	57	57	56	
IV	28	16	14	11	10	
Charlson comorbidity index, %						<0.001
0	14	22	25	26	26	
1	11	12	13	17	18	
2	16	22	23	20	22	
3	17	15	11	11	12	
4+	42	29	28	27	21	
Medical history, %						
Cardiovascular disease	72	69	67	71	67	0.14
Pulmonary	18	15	16	17	21	0.10
Digestive disease	50	43	41	43	41	0.003
Chronic renal failure	36	28	21	20	17	<0.001
HIV	1	<1	<1	<1	<1	0.54
Dementia	2	1	1	2	1	0.34
Cancer	26	33	37	37	38	<0.001
Diabetes						<0.001
No diabetes	56	65	71	69	73	
Type I diabetes	5	5	4	6	4	
Type II diabetes, insulin	39	31	26	25	23	
Emergent surgery, %	13	8	8	5	5	<0.001
Type of surgery, %						<0.001
Digestive system	26	26	24	24	22	
Musculoskeletal system	17	19	20	20	24	
Miscellaneous diagnostic and therapeutic procedures	16	7	5	4	4	
Cardiovascular system	11	9	9	7	6	
Urinary system	9	12	11	8	8	
Endocrine system	7	9	9	12	8	
Integumentary system	4	5	7	7	8	
Nervous system	3	4	6	6	5	
Female genital organs	2	4	4	5	5	
Respiratory system	2	2	1	2	3	
Nose, mouth, and pharynx	1	3	1	2	2	
Male genital organs	1	1	1	2	2	
Hemic and lymphatic system	1	1	1	1	2	
Duration of surgery, h	3 [2–6]	3 [2–4]	3 [2–4]	3 [2–4]	3 [2–4]	<0.001

Summary statistics are presented as % of patients, mean ± SD, or median [Q1, Q3], respectively.
ASA = American society of anesthesiologists; HIV = human immunodeficiency virus.
*Pearson's χ^2 test, unless specified.
†ANOVA.
‡Kruskal-Wallis ANOVA by ranks.

date and the date of surgery was 13 [−4, 46] days (i.e., 13 days before surgery). Vitamin D measurements of 1022 (29%) patients were obtained postoperatively; 924 and 727 of them were obtained >2 days and >1 week after surgery, respectively. Table 1 shows the summary statistics of baseline characteristics by the quintiles of serum vitamin D concentration. The Charlson comorbidity index is a summative score based on the concurrent clinical conditions in an individual patient.[23]

Higher vitamin D concentrations were associated with decreased odds of in-hospital mortality/morbidity (P = 0.003). The corresponding common effect OR of vitamin D level across individual in-hospital mortality/morbidity was estimated as 0.93 (95% CI, 0.88–0.97) for a 5-unit increase in vitamin D level (Table 2). The estimated probability of in-hospital mortality/morbidity decreases as vitamin D concentration increases in a rather linear fashion when all data points are plotted,

Table 2. The Associations[a] Between Serum Vitamin D Concentration and In-hospital Outcomes Among 3509 Noncardiac Surgical Adult Patients

In-hospital outcome	Incidence *N* (%)	OR[b] (98.3% CI)[c]	*P*[a]
Mortality	43 (1.2)	0.90 (0.75–1.07)	0.13
Cardiovascular	176 (5.0)	0.92 (0.84–1.00)	0.01
Infectious	245 (7.0)	0.94 (0.86–1.02)	0.07
		OR[b] (95% CI)	
Common effect of vitamin D across the above outcomes[d]		0.93 (0.88–0.97)	0.003

[a]Age, gender, body mass index, race, ASA physical status, Charlson comorbidity index, cardiovascular disease, digestive disease, pulmonary disease, dementia, chronic renal failure, cancer, diabetes, emergent case, type of surgery, and duration of surgery were adjusted for in the analysis.
[b]Odds ratio for a 5 ng/mL increase in vitamin D concentration.
[c]Bonferroni correction was used to adjust for multiple testing. Thus, the 98.3% CIs were reported, and the significance criterion for the 3 primary outcomes was $P < 0.017$ (i.e., 0.05/3).
[d]The associations were homogeneous among the 3 individual in-hospital outcomes (vitamin D-by-outcome interaction, $P = 0.73$).

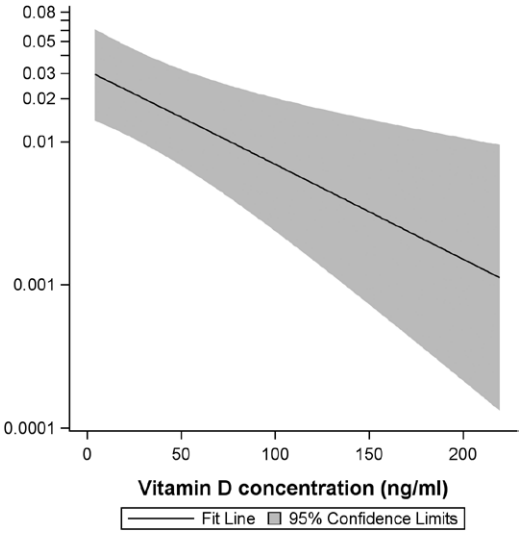

Figure 1. Probability of in-hospital mortality/morbidity (on the logit scale) versus vitamin D concentration. Probabilities were estimated by using multivariate generalized estimating equation model with a smooth term for vitamin D concentration.

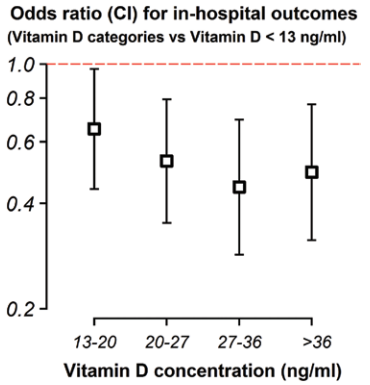

Figure 2. Common effect odds ratio (99% CI) of each quintile of vitamin D concentration (versus the lowest quintile: vitamin D <13 ng/mL) across the individual in-hospital mortality/morbidity with adjusting for the same set of confounders included for the primary analysis. The confidence intervals were adjusted for multiple comparisons by using the Bonferroni correction. The odds versus patients with vitamin D <13 ng/mL were significantly lower in patients with vitamin D 13–20, 20–27, 27–36, and > 36 ng/mL, while the odds did not differ significantly among quintiles with vitamin D >13 ng/mL.

though 97.4% of the values were below 60 ng/mL (Fig. 1).

The associations were homogeneous among the 3 individual in-hospital outcomes (vitamin D-by-outcome interaction, $P = 0.73$). Among the individual outcomes, vitamin D level was significantly associated only with decreased odds of having cardiovascular morbidity (OR: 0.92 [98.3% CI, 0.84–1.00] for a 5-unit increase in vitamin D, $P = 0.01$, Table 2). The raw incidence by quintiles of the vitamin D concentration is provided (Appendix 2).

Although patients who had their vitamin D concentration measured after surgery were different than other patients (Appendix 3), the association between vitamin D concentration and postoperative outcomes was not different (interaction P value = 0.92). Among 1022 patients who had their vitamin D concentration measured postoperatively, the common effect OR of vitamin D concentration across individual in-hospital mortality/morbidity was estimated as 0.92 (95% CI, 0.82–1.03) for a 5-unit increase in vitamin D concentration.

In addition, we found that the odds versus patients with vitamin D <13 ng/mL (i.e., 1st quintile) were significantly lower in patients with vitamin D 13–20, 20–27, 27–36, and >36 ng/mL (i.e., 2nd–5th quintiles); the corresponding estimated odds ratios were 0.65 (99% CI, 0.43–0.98), 0.53 (0.35–0.80), 0.44 (0.28–0.70), and 0.49 (0.31–0.78), respectively. However, there was no statistically significant difference among individual quintiles >13 ng/mL (Fig. 2).

We also observed that mean arterial blood pressure and systolic and diastolic blood pressures were descriptively similar among the groups divided by the quintiles of vitamin D level. Patients in the lowest vitamin D group, on average, were more likely to receive a vasopressor, to receive more red blood cells and colloid, to receive less crystalloid, and to have faster heart rates during surgery (Table 3). However, none of the differences was clinically important.

DISCUSSION

The importance of vitamin D is apparent in that it is one of the few compounds that is both absorbed and produced by the human body. Vitamin D has been associated with multiple human processes for >100 years,[7] though the impact of vitamin D insufficiency and deficiency in biological functions and disease processes is continually being discovered. In our study, higher vitamin D concentrations were associated with decreased odds of in-hospital mortality/morbidity.

The common effect OR for our composite outcome (compared with vitamin D concentrations <13 ng/mL, the lowest

quintile of our study population) was inversely related to serum vitamin D concentration. These results are comparable with studies reviewed in a meta-analysis that found that mortality was inversely related to vitamin D concentration in nonoperative settings.[24] In that summative study, mortality decreased with higher vitamin D concentrations up to 87.5 nmol/L (35 ng/mL), whereas higher concentrations provided no apparent additional benefit.

Our study showed a similar trend: all concentration ranges >13 ng/mL showed a statistically significant decrease in common effect OR compared with the lowest range. Although there was no statistically significant difference among individual groups >13 ng/mL, nonetheless it is reasonable to conclude that there is concentration dependence after evaluating Figure 2, which shows a fairly linear decrease in the estimated common effect ORs as vitamin D concentration increases from the 2nd quintile (13–20 ng/mL) to the 4th quintile (27–36 ng/mL). Our study expands on previous investigations by calculating the marginal decrease of events associated with increasing vitamin D concentrations, but more importantly, our study differs in being perioperative. For each 5 ng/mL increase in vitamin D concentration, there was a reduction of the corresponding common effect OR for the composite outcome (OR 0.93, 95% CI, 0.88–0.97). This remained consistent over the range from 4 to 44 ng/mL, which encompassed 90% of the observed concentrations.

Among the individual components of our composite, only cardiovascular outcomes were significantly associated with decreased odds (OR 0.92, 95% CI, 0.84–1.00), though there were strong trends for infection and mortality. It has been shown that low vitamin D concentrations are associated with an increased probability of these minor outcomes by decreasing innate host defenses.[25] That may have been the case in our patients, but the infection component of our composite was restricted to major infections and thus excluded minor infections such as urinary tract, superficial surgical site, and minor nosocomial infections. Lack of significance on mortality may be related to the relatively low incidence of the event (1.2%).

The only composite component that individually showed significance was cardiovascular complications. Low vitamin D concentrations are associated with increased arterial stiffness and endothelial dysfunction in human blood vessels, which may explain the independent association with cardiovascular mortality.[26,27] In addition, animal studies show that vitamin D deficiency causes deregulated stimulation of the renin-angiotensin system, leading to hypertension.[28]

The relationship between vitamin D levels and the odds of having a common effect outcome clearly shows an association, but causation cannot be claimed. There is, however, the possibility of reverse causation. Patients with cardiac problems may spend more time indoors due to limitations on physical activity, in turn diminishing sun exposure and decreasing vitamin D concentrations. Consistent with this theory, previous studies demonstrated that physical activity is closely related to serum vitamin D concentrations.[29,30] Lower vitamin D concentrations are associated with frailty, characterized by decreased strength and endurance measures in older adults. In frail individuals, low vitamin D concentrations have an additive interaction on all-cause mortality.[31] Therefore, regardless of directionality, lower vitamin D concentrations are associated with worse outcomes, as our study illustrates.

Optimal concentrations of serum vitamin D for various populations have been discussed extensively in recent years, resulting in a wide range of (generally increasing) target concentrations. The most common currently accepted definition of vitamin D insufficiency is a 25-hydroxyvitamin D concentration between 10 to 30 ng/mL, with concentrations <10 ng/mL, indicating deficiency.[1] With the use of these definitions, <20% of our study patients were considered vitamin D deficient. However, our first, second, and middle quintiles completely encompass the insufficiency range. Thus, >60% of our study population was either vitamin D deficient or insufficient (Table 3). That each of our 3 lowest quintiles was associated with serious perioperative complications suggests that current guidelines are generally appropriate.

In a previous study,[32] we were unable to demonstrate an association between serum vitamin D concentrations and outcomes after cardiac surgery. There are several potential explanations for this difference. Perhaps, the most obvious is that cardiac surgery involves much more tissue injury and inflammation than most noncardiac surgery; it is possible that vitamin D effects are simply overwhelmed by the insult of cardiac surgery. A second possibility is that hemodilution during cardiopulmonary bypass per se reduces vitamin D concentrations; however, the decrease is transient and resolves within 24 hours.[33] The former explanation thus seems more likely.

Analysis of baseline demographics (Table 1) in our population indicates that the fraction of women increased with vitamin D concentration, as did age. Though a previous investigation reported the opposite trend,[34] the more recent NHANES III investigation found that vitamin D concentrations were similar in men and women and as a function of age.[35] Surgical patients may differ from the NHANES III population; furthermore, our data are more recent. The higher concentrations of vitamin D we observed in Caucasians are consistent with previous studies.[34,35] Lower concentrations of vitamin D observed in diabetics are similarly consistent with previous studies, which also show insulin resistance.[36,37]

An advantage of our study is that we analyzed the 3 outcomes as a composite by using a multivariate analysis that adjusts for the correlations between the outcomes and improves the power as compared with the traditional methods, including analyzing the outcomes as a collapsed composite or separately. There are nonetheless several limitations inherent to retrospective analysis of data. The timing of the vitamin D concentration measurements varied over a range starting 3 months before surgery to 1 month afterwards, although 71% of the samples were obtained before surgery. Though seasonal variations may occur, an individual's vitamin D level remains relatively stable over a 1-year period.[38]

A post hoc analysis limited to postoperative vitamin D concentrations shows a similar common effect OR 0.92 for each 5-unit increase in vitamin D concentration. We have

Table 3. Intraoperative Hemodynamic Characteristics for 3509 Noncardiac Surgical Patients by Quintiles of Serum Vitamin D Concentration

	Serum vitamin D concentration (ng/mL)				
Variable	**≤13, (*N* = 702)**	**13.1–20.4, (*N* = 709)**	**20.5–27.3, (*N* = 711)**	**27.4–36.2, (*N* = 692)**	**>36.2, (*N* = 695)**
Red blood cell, L	0 [0–0.4]	0 [0–0]	0 [0–0]	0 [0–0]	0 [0–0]
Crystalloid, L	0.6 [0.0–1.5]	1.0 [0.0–1.6]	1.0 [0.0–1.7]	1.0 [0.1–1.6]	1.1 [0.5–1.7]
Colloid, L	0 [0.0–0.7]	0 [0.0–0.5]	0 [0.0–0.5]	0 [0.0–0.5]	0 [0.0–0.5]
Heart rate, beats/min					
Average	79 ± 14	75 ± 12	74 ± 13	74 ± 12	74 ± 14
Standard deviation	8 [5–10]	8 [6–10]	8 [5–10]	7 [5–10]	8 [5–10]
Mean arterial blood pressure, mm·Hg					
Average	83 ± 13	84 ± 11	85 ± 12	84 ± 11	84 ± 11
Standard deviation	13 [10–16]	13 [10–17]	13 [10–17]	13 [10–17]	13 [10–16]
Systolic blood pressure, mm·Hg					
Average	114 [105–129]	116 [106–127]	116 [107–128]	116 [106–128]	115 [105–128]
Standard deviation	19 ± 7	19 ± 8	19 ± 7	18 ± 7	18 ± 7
Diastolic blood pressure, mm·Hg					
Average	63 ± 11	64 ± 10	65 ± 10	64 ± 9	64 ± 9
Standard deviation	10 [8–12]	10 [8–13]	10 [8–12]	10 [8–12]	9 [7–12]
Vasopressor (yes), %	59	51	50	46	48

Summary statistics was presented as mean ± SD or median [Q1, Q3], as appropriate.

no way of knowing the specific indications, preoperatively or postoperatively, for which the vitamin D levels were evaluated. We cannot deny possible selection bias in which patients were tested in this retrospective study. Indeed, patients with postoperative vitamin D measurements, compared with the preoperative measurement group, were sicker as indicated by physical status class, Charlson comorbidity index, and need for emergency surgery. Patients without vitamin D measurements were not included in the study, which theoretically may be healthier patients. Admittedly, the mean and median vitamin D levels may be different than other populations in other locations. Multiple variables were accounted for in the analysis to adjust for potential confounders to address this concern. We also do not know whether low vitamin D concentrations were treated or how effective the treatments might have been. It is thus possible that actual serum concentrations at the time of surgery were higher than the values used in our analysis. However, with varying vitamin D repletion protocols, it can take up to 9 months to reach adequate concentrations.[39] It thus seems unlikely that acute treatment, even if provided, would much alter serum concentration in our patients. Due to the relative stability of 25-hydroxyvitamin D concentrations, we included both preoperative and postoperative measurements in our study. Only a small portion of noncardiac surgical patients had 25-hydroxyvitamin D measurements and were included in this study. We have no information as to why these patients had their vitamin D levels measured and thus how this patient selection may have influenced our results; results may differ in other settings and other populations.

To the extent that vitamin D supplementation was instituted and effective, it would reduce the apparent association of low concentrations with adverse outcomes. However, the effect of supplementation of vitamin D levels on outcomes remains questionable.[40] Furthermore, treatment was presumably most likely in patients with the lowest concentrations, which would further reduce the apparent concentration dependence of our findings. But even with the possibility of treatment, our results remain highly statistically significant and show clinically important concentration dependence over the entire range of observed values.

Adjustments in the multivariate analysis were made for known confounders for the components of common effect such as baseline demographics and intraoperative variables. But surely, there remain unknown factors that could have substantial impact on the results. Data for this study were collected from the Cleveland Clinic Perioperative Health Documentation System, exclusively representing the Clinic's Main Campus hospitals. However, the Cleveland Clinic is a tertiary care hospital, drawing patients from around the country and around the world, and the results can presumably at least be generalized to other tertiary centers. Geography is an important factor in determining average vitamin D concentrations. Cleveland is not among the sunniest cities, making it difficult to generalize average

Appendix 1. Definition and Incidence of Individual Cardiovascular and Infectious Morbidities Included in the Composite

Outcome	Description	ICD-9	Incidence (%)
Cardiovascular complications	Cardiac complications	997.1	49 (1.4)
	Cardiac:		
	Arrest during or resulting from a procedure		
	Insufficiency during or resulting from a procedure		
	Cardiorespiratory failure during or resulting from a procedure		
	Heart failure during or resulting from a procedure		
	Peripheral vascular complications	997.2	19 (0.54)
	Phlebitis or thrombophlebitis during or resulting from a procedure		
	Postoperative shock	998.0	29 (0.83)
	Collapse NOS during or resulting from a surgical procedure		
	Shock (endotoxic) (hypovolemic) (septic) during or resulting from a surgical procedure		
	Acute edema of lung, unspecified	518.4	11 (0.31)
	Acute pulmonary edema NOS		
	Pulmonary edema, postoperative		
	Hypotension of hemodialysis	458.21	6 (0.17)
	Intradialytic hypotension		
	Other iatrogenic hypotension	458.29	87 (2.48)
	Postoperative hypotension		
	Any of the above		176 (5.0)
Infectious complications	Infection and inflammatory reaction due to internal prosthetic device, implant, and graft:	996.60	6 (0.17)
	Infection (causing obstruction)/inflammation due to (presence of) any device, implant, and graft	996.61	27 (0.77)
		996.62	3 (0.09)
		996.63	10 (0.28)
		996.64	2 (0.06)
		996.65	20 (0.57)
		996.66	9 (0.26)
		996.67	7 (0.20)
		996.68	18 (0.51)
		996.69	
	Ventilator associated pneumonia	997.31	8 (0.23)
	Other respiratory complications	997.39	10 (0.28)
	Mendelson's syndrome resulting from a procedure		
	Pneumonia (aspiration) resulting from a procedure		
	Infected postoperative seroma	998.51	1 (0.03)
	Other postoperative infection	998.59	109 (3.11)
	Abscess:		
	Postoperative		
	Intra-abdominal postoperative		
	Stitch postoperative		
	Subphrenic postoperative		
	Wound postoperative		
	Septicemia postoperative		
	Other infection	999.31	36 (1.03)
	Infection/Sepsis/Septicemia following infusion, injection, transfusion, or vaccination		
	Due to central venous catheter:		
	Catheter-related bloodstream infection (CRBSI) NOS		
	Due to:		
	Hickman catheter		
	Peripherally inserted central catheter (PICC)		
	Portacath (port-a-cath)		
	Triple lumen catheter		
	Umbilical venous catheter		
	Infection of tracheostomy	519.01	2 (0.06)
	Infection of esophagostomy	530.86	0 (0)
	Infection of gastrostomy	536.41	0 (0)
	Infection of colostomy and enterostomy	569.61	5 (0.14)
	Amputation stump complication: infection (chronic)	997.62	4 (0.11)
	Any of the above		245 (7.0)

Appendix 2. Incidence of In-hospital Mortality Cardiovascular and Infectious Morbidities for 3509 Noncardiac Surgical Patients by Quintiles of Serum Vitamin D Concentration

	Serum vitamin D concentration (ng/mL)				
In-hospital outcome	**≤13, (*N* = 702)**	**13.1–20.4, (*N* = 709)**	**20.5–27.3, (*N* = 711)**	**27.4–36.2, (*N* = 692)**	**>36.2 (*N* = 695)**
Mortality	19 (2.7%)	8 (1.1%)	4 (0.6%)	6 (0.9%)	6 (0.9%)
Cardiovascular	67 (9.5%)	38 (5.4%)	29 (4.1%)	20 (2.9%)	22 (3.2%)
Infectious	93 (13.3%)	46 (6.5%)	38 (5.3%)	36 (5.2%)	32 (4.6%)

Appendix 3. Demographics and Baseline Medical Conditions for Patients with Vitamin D Concentration Measured Before and After Surgery[41]

	Patients with vitamin D measured before surgery, (*N* = 2487)	**Patients with vitamin D measured after surgery, (*N* = 1022)**	**STD***
Age, y	58 ± 15	58 ± 16	0.02
Gender (male), %	38	44	0.11
Race, %			0.03
Caucasian	20	19	
African American	75	76	
Others	5	5	
Body mass index, kg/m^2	28 [24–34]	27 [23–32]	0.18
ASA physical status, %			0.22
I	1	2	
II	27	22	
III	58	57	
IV	14	20	
Charlson comorbidity index, %			0.18
0	24	19	
1	15	13	
2	21	19	
3	13	14	
4+	27	34	
Medical history, %			
Cardiovascular disease	70	66	0.09
Pulmonary	18	17	0.03
Digestive disease	45	42	0.06
Chronic renal failure	23	28	0.12
HIV	<1	<1	0.02
Dementia	1	1	0.02
Cancer	34	36	0.05
Diabetes			0.02
No diabetes	67	66	
Type I diabetes	5	5	
Type II diabetes, insulin	28	29	
Emergent surgery, %	6	12	0.19
Type of surgery, %			0.37
Digestive system	27	20	
Musculoskeletal system	20	18	
Miscellaneous diagnostic and therapeutic procedures	5	13	
Cardiovascular system	9	7	
Urinary system	8	12	
Endocrine system	9	10	
Integumentary system	6	6	
Nervous system	5	4	
Female genital organs	4	3	
Respiratory system	2	2	
Nose, mouth, and pharynx	2	2	
Male genital organs	2	1	
Hemic and lymphatic system	1	2	
Duration of surgery, h	3 [2–5]	3 [2–4]	0.24

Standardized difference is the difference in means or proportions divided by the pooled standard deviation. 0.2, 0.5, and 0.8 to represent small, medium, and large standardized differences in absolute values.

ASA = American society of anesthesiologists; HIV = human immunodeficiency virus; STD = standardized difference.

vitamin D results. However, the concentration dependence we observed is presumably valid.

In summary, vitamin D concentrations were associated with a composite of in-hospital death, serious infections, and serious cardiovascular events. However, vitamin D levels were presumably not obtained randomly; therefore, a large randomized trial of preoperative vitamin D supplementation and postoperative outcomes is justified.

DISCLOSURES

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Attestation: Alparslan Turan has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
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