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CLINICAL ARTICLE

A prospective analysis of hypovitaminosis D and mortality in 400 patients in the neurocritical care setting

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OBJECTIVE Hypovitaminosis D is highly prevalent among the general population. Studies have shown an association between hypovitaminosis D and multiple negative outcomes in critical care patients, but there has been no prospective evaluation of vitamin D in the neurological critical care population. The authors examined the impact of vitamin D deficiency on in-hospital mortality and a variety of secondary outcomes.

METHODS The authors prospectively collected 25-hydroxy vitamin D levels of all patients admitted to the neurocritical care unit (NCCU) of a quaternary-care center over a 3-month period. Demographic data, illness acuity, in-hospital mortality, infection, and length of hospitalization were collected. Univariate and multivariable logistic regression were used to examine the effects of vitamin D deficiency.

RESULTS Four hundred fifteen patients met the inclusion criteria. In-hospital mortality was slightly worse (9.3% vs 4.5%; p = 0.059) among patients with deficient vitamin D (≤ 20 ng/dl). There was also a higher rate of urinary tract infection in patients with vitamin D deficiency (12.4% vs 4.2%; p = 0.002). For patients admitted to the NCCU on an emergency basis (n = 285), higher Simplified Acute Physiology Score II (OR 13.8, 95% CI 1.7–110.8; p = 0.014), and vitamin D deficiency (OR 3.0, 95% CI 1.0–8.6; p = 0.042) were significantly associated with increased in-hospital mortality after adjusting for other factors.

CONCLUSIONS In the subset of patients admitted to the NCCU on an emergency basis, vitamin D deficiency is significantly associated with higher in-hospital mortality. Larger studies are needed to confirm these findings and to investigate the role of vitamin D supplementation in these patients.

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KEY WORDS vitamin D; mortality; prospective study; multivariable analysis; risk factors; hypovitaminosis; trauma

Hypovitaminosis D has a high prevalence among the general population, with some studies showing that more than half of the elderly are affected.[7,13,16] First reported in 2009 as a potential marker of poor outcome in the critical care population,[22] hypovitaminosis D has been shown to be associated with various negative outcomes, including mortality,[11,30,32] acute respiratory distress syndrome,[10] and infection.[12] A recent randomized trial showed reduced in-hospital mortality in patients with severe vitamin D deficiency (≤ 12 ng/ml) who received vitamin D supplementation.[1] Vitamin D deficiency has also been shown to have an effect on immune, inflammatory, cardiac, and vascular functions,[17] including various neurological diseases such as stroke[8,34] and dementia.[23]

Despite the important role of vitamin D, there have been no studies examining the impact of hypovitaminosis D in patients in specialized neurocritical care units (NCCUs). Given the significant differences in management of patients between NCCUs and more generalized ICUs,[20] there is a need for further inquiries into the impact of low vitamin D levels in this specific environment. We prospectively studied the association between hypovitaminosis D and mortality and other secondary outcomes at a quaternary NCCU.

Methods

Study Population

Approval from the University of Utah Institutional Review Board was obtained prior to initiation of this study and included a waiver of informed consent. Data on 25-hy-

ABBREVIATIONS BMI = body mass index; GCS = Glasgow Coma Scale; NCCU = neurocritical care unit; SAPS II = Simplified Acute Physiology Score.

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droxy vitamin D levels and other patient variables were prospectively gathered using clinical examinations, review of radiological films, and evaluation of the medical record.

Data Collection

All patients admitted to the University of Utah Hospital NCCU between September 1, 2015, and December 1, 2015, were eligible for enrollment in the study. A waiver of informed consent was obtained for this study because patients routinely undergo vitamin D testing in our NCCU, and enrollment in the study involved no more than minimal risk. Patients were excluded if they were younger than 18 years at the time of admission, were admitted under a service other than neurosurgery or neurology because of hospital intensive care bed needs, or were unable to have vitamin D levels checked within 24 hours of admission to the NCCU. Patients who were readmitted to the NCCU prior to discharge were not dual enrolled.

Baseline demographic information including age, sex, body mass index (BMI), insurance type (divided into private, Medicaid/self-pay, and Medicare), and race/ethnicity was obtained when available. The presence of hypertension and diabetes was recorded for each patient, in addition to tobacco, alcohol, and illicit drug use. Admission information including admission Glasgow Coma Scale (GCS) score, whether there was surgical intervention immediately prior to or during NCCU admission, and whether the admission was elective or due to an emergency was also recorded. The GCS score was determined by the NCCU attending surgeon at the time of admission in patients who were not sedated. In patients who were sedated at admission, chart review of physician notes was performed to obtain the last available GCS score prior to the initiation of sedation. Finally, in patients who were sedated prior to hospital arrival or who underwent procedures that could alter their GCS status immediately before admission, the GCS score was determined based on chart review to obtain the recorded GCS score 1 hour after cessation of sedation. Elective admissions included patients who were scheduled for ICU admission > 1 week prior to arrival in the ICU, including those for prearranged cranial or spine procedures or planned diagnostic testing. Admission diagnosis was separated into 4 categories: postoperative, stroke (hemorrhagic and ischemic), trauma, and other.

Each patient had a Simplified Acute Physiology Score (SAPS II) calculated per established guidelines and within 48 hours of NCCU admission.[21] The SAPS II is an instrument that uses 17 variables including physiological, demographic, and hospitalization-specific factors. The score was derived using an international sample of patients as a tool for calculating the probability of in-hospital mortality irrespective of primary admission diagnosis. The SAPS II has shown efficacy in the NCCU setting[26] and in patients with diagnoses that are commonly seen in the NCCU, including stroke,[14,25] subarachnoid hemorrhage,[31] and traumatic brain injury.[29]

All 25-hydroxy vitamin D levels were obtained within 24 hours of NCCU admission. In addition to 25-hydroxy vitamin D levels, serum calcium levels (mg/dl) and phosphate levels (mg/dl) were recorded when available if obtained within 24 hours of NCCU admission. These were dichotomized into "high" and "low" groups based on normal values (3.25 mg/dl for phosphate level, 9.35 mg/dl for calcium level).[27] In cases where > 1 laboratory value was obtained, the value closest to the time of NCCU admission was used. Five patients had missing phosphate levels, and the median phosphate value (3.3 mg/dl) was substituted for multivariable analysis in these cases. Preadmission vitamin D supplementation, defined as daily supplemental intake > 500 U, was also recorded. Patients who were on vitamin D supplementation prior to hospitalization were not continued on supplementation as inpatients, although those who were found to be deficient in vitamin D were treated using 50,000 U of vitamin D administered orally or via feeding tube weekly, per hospital protocol.

The primary outcome for this study was in-hospital mortality. Secondary outcome measures, including ventilator duration, NCCU length of stay, and hospital length of stay, were recorded for all patients. Information regarding the presence or development of urinary tract infection, pneumonia, or sepsis during the hospital stay was also obtained. Infection in all cases was defined as culture-positive evidence of infection requiring subsequent treatment with antibiotic therapy.

Statistical Analysis

Continuous variables in all cases were analyzed using the Student t-test, and categorical variables were analyzed using chi-square analysis with correction for multiple comparisons. Univariate analysis was performed for vitamin D status after patients were dichotomized into vitamin D–deficient (25-hydroxy vitamin D level ≤ 20 ng/dl) and vitamin D–nondeficient (25-hydroxy vitamin D level > 20 ng/dl) groups based on previously published cutoffs.[18,24] Univariate and multivariable logistic regression analysis was performed on in-hospital mortality. Our multivariable model included all variables with a $p < 0.2$ on our univariate analysis with the exception of age and GCS score (because these are components of the SAPS II), and with the addition of insurance type, sepsis, and urinary tract infection. The SAPS II results were dichotomized for multivariable analysis based on a median SAPS II of 23 for the cohort. All analyses were performed on the entire patient cohort as well as on a subgroup of patients who were emergency admissions to the NCCU. In all cases, variables that demonstrated $p < 0.05$ in all cases were deemed to be statistically significant.

Results

Of 461 unique admissions to the NCCU during the study period, 415 met criteria for inclusion. Approximately 9% of screened patients (n = 46) were excluded because they were admitted to a non–neurology/neurosurgery service (n = 19), were younger than 18 years (n = 4), were readmitted during the same hospitalization (n = 14), and/or lacked 25-hydroxy vitamin D levels obtained within 24 hours of admission (n = 9). There were 129 patients with deficient 25-hydroxy vitamin D levels (31.1%) and 286 patients with nondeficient levels (68.9%). On univariate analysis (Table 1), vitamin D–deficient patients were younger (53.1 ± 17.2 vs 57 ± 19.4 years; $p = 0.05$), had higher BMI (29.2 ± 7.6 vs

TABLE 1. Univariate analysis of 25-hydroxy vitamin D–deficient versus nondeficient patients*

Variable	Deficient, n = 129	Nondeficient, n = 286	p Value†
Mean age in yrs ± SD	53.08 ± 17.16	56.98 ± 19.36	0.050
Female	61 (47.3)	126 (44.1)	0.540
Hypertension	59 (45.7)	129 (45.1)	0.905
Diabetes	26 (20.2)	41 (14.3)	0.136
Tobacco use	24 (18.6)	55 (19.2)	0.880
Alcohol use	43 (33.3)	106 (37.1)	0.464
Illicit drug use	7 (5.4)	24 (8.4)	0.288
Vitamin D supplementation	10 (7.8)	75 (26.2)	<0.001
GCS score ± SD	12.79 ± 3.36	13.00 ± 3.09	0.528
SAPS II ± SD	26.49 ± 16.25	25.33 ± 13.84	0.457
BMI ± SD	29.24 ± 7.59	27.44 ± 6.08	0.010
High calcium level	17 (13.2)	58 (20.3)	0.082
High phosphate level	70 (54.3)	142 (49.7)	0.384
Planned admission	35 (27.1)	95 (33.2)	0.216
Surgery during NCCU stay	62 (48.1)	166 (58.0)	0.059
Insurance type			<0.001
Private	67 (51.9)	123 (43.0)	
Medicaid/self-pay	35 (27.1)	37 (12.9)	
Medicare	27 (20.9)	126 (44.1)	
Admission category			0.075
Postop	34 (26.4)	95 (33.2)	
Trauma	16 (12.4)	44 (15.4)	
Stroke	41 (31.8)	58 (20.3)	
Other	38 (29.5)	89 (31.1)	
Race/ethnicity			0.207
White	103 (79.8)	253 (88.5)	
Hispanic/Latino	10 (7.8)	14 (4.9)	
African American	4 (3.1)	4 (1.4)	
Asian/Pacific Islander	6 (4.7)	5 (1.7)	
Native American	3 (2.3)	3 (1.0)	
Other/unknown	3 (2.3)	7 (2.4)	
Length of NCCU stay in days ± SD	3.50 ± 4.12	3.36 ± 4.17	0.751
Length of hospital stay in days ± SD	6.74 ± 7.28	5.73 ± 5.94	0.137
Ventilator duration in days ± SD	1.23 ± 3.59	1.08 ± 4.54	0.731
Urinary tract infection	16 (12.4)	12 (4.2)	0.002
Pneumonia	10 (7.8)	13 (4.5)	0.186
Sepsis	3 (2.3)	2 (0.7)	0.160
In-hospital mortality	12 (9.3)	13 (4.5)	0.059

* Unless otherwise indicated, values represent number of patients (%).
† $p < 0.05$ considered significant.

27.4 ± 6.1; p = 0.01), were more likely to have no insurance or be reliant on Medicaid (27.1% vs 12.9%; p < 0.001), and were less likely to be on vitamin D supplementation (7.8% vs 26.2%; p < 0.001). Patients in the deficient group were also more likely to be diagnosed with a urinary tract infection during the hospitalization (12.4% vs 4.2%; p = 0.002). Other variables were not significantly different between deficient and nondeficient groups, including length of NCCU stay (3.5 ± 4.1 vs 3.4 ± 4.2 days; p = 0.751), length of hospital stay (6.7 ± 7.3 vs 5.7 ± 5.9 days; p = 0.137), and in-hospital mortality (9.3% vs 4.5%; p = 0.059).

An analysis of in-hospital mortality for all NCCU and emergency admissions was performed (Table 2). The in-hospital mortality rate for the full cohort of NCCU patients was 6.0%, whereas that for emergency admissions alone was 7.7%. A comparison of all NCCU patients showed that those who died in the hospital were more likely to be older (63.8 ± 14.2 vs 55.3 ± 18.9 years; p = 0.027), to have a longer NCCU stay (5.6 ± 6 vs 3.3 ± 4 days; p = 0.005), and to have a lower admission GCS score (8.4 ± 4.1 vs 13.2 ± 2.9; p < 0.001). They were also more likely to have a higher calculated SAPS II (50 ± 14.8 vs 24.1 ± 13.2; p < 0.001), to be on a ventilator longer (4.7 ± 5.7 vs 0.9 ± 4.1 days; p < 0.001), to be an emergency admission (88% vs 67.4%; p = 0.032), and to have developed pneumonia during their hospitalization (24% vs 4.4%; p < 0.001). On multivariable regression analysis, only higher SAPS II remained significantly associated with in-hospital mortality (OR 24.4, 95% CI 2.9–200) (Table 3).

A subgroup analysis of in-hospital mortality in only patients who were emergency admissions (n = 285) was also performed (Table 4). Patients in this group who died also had a lower admission GCS score (8.3 ± 4.1 vs 13 ± 3.1; p < 0.001), higher calculated SAPS II (50 ± 14.7 vs 27.9 ± 13.1; p < 0.001), and longer ventilator duration (3.8 ± 4.6 vs 1.1 ± 3.5 days; p = 0.001). They were also significantly more likely to have vitamin D deficiency (54.5% vs 31.2%; p = 0.025). In addition, pneumonia rates during hospitalization were higher in patients with vitamin D deficiency (18.2% vs 6.1%; p = 0.033). On multivariable regression analysis, both higher SAPS II (OR 13.8, 95% CI 1.7–110.8) and vitamin D deficiency (OR 3.0, 95% CI 1.0–8.6) remained significantly associated with in-hospital mortality in patients who were unscheduled admissions to the NCCU.

Discussion

To our knowledge, this is the first investigation of the association of hypovitaminosis D and mortality in the neurocritical care population, as well as one of the largest prospective examinations of the topic in any critical care patient group. Our model indicates that the in-hospital mortality rate of patients who were admitted to the NCCU in an unscheduled fashion who had vitamin D deficiency was 3 times higher than that of their peers without vitamin D deficiency. Although there was a strong trend toward higher in-hospital mortality in our entire cohort for patients with vitamin D deficiency, the difference was not statistically significant on multivariable logistic regression analysis (p = 0.155). It is possible that this was due to the extremely low mortality rate among patients who were scheduled admissions to our NCCU: only 3 patients of 130 with scheduled admissions died, a rate of 2.3%.

Our results are in agreement with previously published reports in medical and surgical ICU settings showing that

TABLE 2. Univariate analysis of in-hospital mortality*

Variable	All Patients			Emergency Admissions		
	No Mortality, n = 390	Mortality, n = 25	p Value†	No Mortality, n = 263	Mortality, n = 22	p Value†
Mean age in yrs ± SD	55.25 ± 18.92	63.80 ± 14.24	0.027	56.49 ± 19.97	62.73 ± 14.62	0.153
Female	178 (45.6)	9 (36)	0.348	111 (42.2)	8 (36.4)	0.594
Hypertension	173 (44.4)	15 (60)	0.128	127 (48.3)	13 (59.1)	0.330
Diabetes	62 (15.9)	5 (20)	0.589	47 (17.9)	4 (18.2)	0.971
Tobacco use	74 (19)	5 (20)	0.899	56 (21.3)	5 (22.7)	0.875
Alcohol use	140 (35.9)	9 (36)	0.992	90 (34.2)	9 (40.9)	0.527
Illicit drug use	29 (7.4)	2 (8)	0.917	22 (8.4)	2 (9.1)	0.906
Vitamin D supplementation	81 (20.8)	4 (16)	0.567	50 (19)	3 (13.6)	0.534
GCS score ± SD	13.23 ± 2.88	8.36 ± 4.05	<0.001	12.95 ± 3.14	8.27 ± 4.11	<0.001
SAPS II ± SD	24.14 ± 13.18	49.96 ± 14.76	<0.001	27.87 ± 13.07	50.00 ± 14.70	<0.001
BMI ± SD	27.98 ± 6.67	28.19 ± 6.16	0.880	27.60 ± 6.55	27.51 ± 5.98	0.947
Vitamin D deficiency	117 (30)	12 (48)	0.059	82 (31.2)	12 (54.5)	0.025
High calcium level	320 (82.1)	20 (80)	0.796	55 (20.9)	5 (22.7)	0.841
High phosphate level	187 (47.9)	16 (64)	0.120	130 (49.4)	7 (31.8)	0.112
Planned admission	127 (32.6)	3 (12)	0.032	NA	NA	NA
Surgery during NCCU stay	217 (55.6)	11 (44)	0.257	90 (34.2)	8 (36.4)	0.839
Insurance type			0.477			0.863
Private	181 (46.4)	9 (36)		106 (40.3)	8 (36.4)	
Medicaid/self-pay	68 (17.4)	4 (16)		53 (20.2)	4 (18.2)	
Medicare	141 (36.2)	12 (48)		104 (39.5)	10 (45.5)	
Admission category			0.001			0.777
Postop	126 (32.3)	3 (12)		9 (3.4)	0 (0)	
Trauma	56 (14.4)	4 (16)		56 (21.3)	4 (18.2)	
Stroke	85 (21.8)	14 (56)		84 (31.9)	14 (63.6)	
Other	123 (31.5)	4 (16)		114 (43.3)	4 (18.2)	
Race/ethnicity			0.534			0.578
White	335 (85.9)	21 (84)		223 (84.8)	18 (81.8)	
Hispanic/Latino	21 (5.4)	3 (12)		15 (5.7)	3 (13.6)	
African American	7 (1.8)	1 (4)		7 (2.7)	1 (4.5)	
Asian/Pacific Islander	11 (2.8)	0 (0)		7 (2.7)	0 (0)	
Native American	6 (1.5)	0 (0)		4 (1.5)	0 (0)	
Other/unknown	10 (2.6)	0 (0)		7 (2.7)	0 (0)	
Length of NCCU stay in days ± SD	3.26 ± 3.98	5.64 ± 6.00	0.005	3.84 ± 4.44	4.41 ± 4.06	0.564
Length of hospital stay in days ± SD	5.97 ± 6.27	7.20 ± 8.114	0.354	6.59 ± 6.28	6.09 ± 7.36	0.724
Ventilator duration in days ± SD	0.90 ± 4.06	4.68 ± 5.65	<0.001	1.10 ± 3.53	3.82 ± 4.62	0.001
Urinary tract infection	25 (6.4)	3 (12)	0.280	21 (8)	2 (9.1)	0.855
Pneumonia	17 (4.4)	6 (24)	<0.001	16 (6.1)	4 (18.2)	0.033
Sepsis	5 (1.3)	0 (0)	0.569	5 (1.9)	0 (0)	0.514

NA = not applicable.

* Unless otherwise indicated, values represent number of patients (%).

† $p < 0.05$ considered significant.

vitamin D deficiency is associated with increased mortality.[2,5,6] The association between vitamin D deficiency and increased mortality is probably multifactorial. Vitamin D deficiency was associated with an increased rate of urinary tract infection in our patient cohort, and there was a trend toward higher rates of both pneumonia and sepsis. This is in keeping with prior studies that have demonstrated an association between low vitamin D levels and poor immune function in the critically ill.[12,15] This is possibly related to the diverse roles that vitamin D plays in the immune process, ranging from the development of naïve T cells into Th2 cells[4] to effects on macrophage function.[19] Vitamin D has also been shown to play an important role in airway inflammation and smooth-muscle function, an

TABLE 3. Multivariable logistic regression of in-hospital mortality among all patients

Variable	B Statistic	OR (95% CI)	p Value*
Length of NCCU stay	−0.068	0.934 (0.818–1.066)	0.312
High SAPS II	3.200	24.4 (2.890–200)	0.003
Ventilator duration	0.068	1.070 (0.975–1.174)	0.154
Vitamin D deficiency	0.727	2.068 (0.760–5.626)	0.155
High phosphate level	0.516	1.675 (0.632–4.442)	0.300
Planned admission	−0.239	0.787 (0.040–15.479)	0.875
Insurance type			0.856
Private	0 (ref)	1.000 (ref)	
Medicaid/self-pay	0.308	1.361 (0.460–4.029)	
Medicare	0.179	1.196 (0.285–5.024)	
Admission category			0.129
Other	0 (ref)	1.000 (ref)	
Postop	0.446	1.561 (0.075–32.390)	
Trauma	0.982	2.670 (0.586–12.163)	
Stroke	1.475	4.372 (1.289–14.834)	
Hypertension	−0.022	0.978 (0.382–2.505)	0.964
Pneumonia	−0.935	0.267 (0.075–2.047)	0.267
Urinary tract infection	0.358	1.430 (0.319–6.417)	0.641
Sepsis	18.954	170,397,151 (NA)	0.999

Ref = reference.
* p < 0.05 considered significant.

TABLE 4. Multivariable logistic regression of in-hospital mortality among emergency admissions

Variable	B Statistic	OR (95% CI)	p Value*
High SAPS II	2.621	13.745 (1.705–110.810)	0.014
Ventilator duration	0.079	1.082 (0.971–1.206)	0.154
Vitamin D deficiency	1.096	2.992 (1.042–8.589)	0.042
High phosphate level	0.561	1.752 (0.620–4.952)	0.290
Insurance type			0.931
Private	0 (ref)	1.000 (ref)	
Medicaid/self-pay	0.163	1.177 (0.367–3.776)	
Medicare	−0.102	0.903 (0.216–3.775)	
Admission category			0.165
Other	0 (ref)	1.000 (ref)	
Postop	−17.079	0.00 (NA)	
Trauma	0.982	2.670 (0.595–11.981)	
Stroke	1.382	3.984 (1.199–13.233)	
Pneumonia	0.252	1.287 (0.215–7.695)	0.782
Urinary tract infection	0.948	2.580 (0.408–16.316)	0.314
Sepsis	18.795	145,399,025 (NA)	0.999

* p < 0.05 considered significant.

especially important factor in ICU patients who are frequently on ventilation.[3] Finally, low levels of vitamin D have been associated with increased rates of cardiovascular disease.[33]

Risk factors for vitamin D deficiency in our cohort are similar to those that have been previously reported.[9,17] Higher BMI was associated with lower vitamin D level, probably because of the sequestration of vitamin D in the fatty tissues of obese patients. Although there was no significant difference in ethnic background between the vitamin D–deficient and –nondeficient groups, this is possibly a result of the low proportion of nonwhite patients in our study cohort. Indeed, when our cohort was instead divided into white and nonwhite groups and a separate statistical analysis was performed, there was a statistically higher proportion of white patients in the nondeficient group ($p = 0.023$). This difference is thought to be due to absorption of sunlight by melanin in the skin of nonwhites, decreasing the production of vitamin D in these groups. Patients on preadmission vitamin D supplementation were also significantly less likely to be deficient in vitamin D, supporting the fact that such supplementation is effective. Patients without insurance and those with Medicaid assistance were also significantly more likely to be deficient in vitamin D. This is possibly due to insurance status being a marker of socioeconomic status, with evidence supporting the finding that patients within lower socioeconomic strata have poorer nutritional intake and, thus, a higher risk for vitamin D deficiency.[28]

Although our study shows a significant association of vitamin D deficiency with in-hospital mortality in unscheduled admissions to the NCCU, there remains a need for further inquiry into how best to manage hypovitaminosis D. There is a lack of high-quality, randomized controlled trials examining the impacts of vitamin D supplementation on outcomes in the critically ill, especially data specific to the neurocritical care population. One clinical trial showed that vitamin D supplementation decreased in-hospital mortality in patients with severe vitamin D deficiency (≤ 12 ng/ml).[1] Such an investigation has not yet been performed in the neurological patient population. This evidence is needed to determine how best to manage these patients and to better elucidate whether the association between hypovitaminosis D and mortality is causative in nature.

Patients in our cohort with severe vitamin D deficiency (< 12 ng/ml) had higher rates of in-hospital mortality than those with moderately deficient vitamin D (12–20 ng/ml, 10.3% vs 9.0%) and those with nondeficient vitamin D (> 20 ng/ml, 10.3% vs 4.5%). This difference was also seen when only looking at emergency NCCU admissions, with severely deficient patients in this subgroup having an in-hospital mortality rate of 15% versus 12.2% for moderately deficient and 5.2% for nondeficient patients. None of these differences, however, reached statistical significance. The reason for this is probably the low number of patients who met criteria for such severe deficiency—only 29 in total. Our vitamin D–deficient group also showed a significantly higher rate of urinary tract infections and a trend toward higher rates of both pneumonia and sepsis. Because of the fairly low rates of infection in our patient cohort, it is difficult to make any conclusions based on these findings, but larger studies in the NCCU may show that vitamin D has more wide-ranging associations with infectious morbidities.

Our study has several limitations. The first is that it is limited to a single institution. Although our patient cohort

is one of the largest among prospective trials investigating this topic, our patient population remains relatively small. These factors limit the generalizability of our findings. The relatively low incidence of in-hospital mortality in our patient cohort as a whole, and especially in those patients who were admitted electively, makes definitive conclusions regarding the impact of vitamin D levels on these patients difficult. Further investigations using pooled data from multiple centers could conceivably overcome these limitations, and it is our hope that our study will provide preliminary evidence to provoke further interest in this topic. We also did not investigate long-term mortality in our study, and it is therefore difficult to say whether vitamin D has any impact on postdischarge outcomes. Finally, providing supplementation for our patients who were found to be deficient in vitamin D may have introduced further confounding into our study, although we would expect that attempting to normalize hypovitaminosis D in our deficient patients would tend to bias us more toward the null hypothesis.

Conclusions

This study demonstrates that vitamin D deficiency in patients admitted on an emergency basis to the NCCU is associated with higher mortality, suggesting that these patients may benefit from closer monitoring during their NCCU stay. The role of vitamin D supplementation in these patients warrants further investigation to determine whether such treatment could improve outcomes in this patient population.

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Disclosures

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Conception and design: Park, Guan, Karsy, Ledyard, Hawryluk. Acquisition of data: Guan, Karsy, Brock, Eli. Analysis and interpretation of data: Guan, Karsy. Drafting the article: Park, Guan, Karsy, Brock, Eli. Critically revising the article: Park, Ledyard, Hawryluk. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Park.

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