Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill

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Abstract

Objective—We hypothesized that deficiency in 25-hydroxy vitamin D (25(OH)D) prior to hospital admission would be associated with all cause mortality in the critically ill.

Design—Multicenter observational study of patients treated in medical and surgical intensive care units.

Setting—209 medical and surgical intensive care beds in two teaching hospitals in Boston, Massachusetts

Patients—2,399 patients, age ≥ 18 years, in whom 25(OH)D was measured prior to hospitalization between 1998 and 2009.

Measurements—Pre-admission 25(OH)D was categorized as deficiency in 25(OH)D (≤ 15ng/mL), insufficiency (16–29ng/mL) and sufficiency (≥ 30ng/mL). Logistic regression examined death by days 30, 90 and 365 post-ICU admission, in hospital mortality and blood culture positivity. Adjusted odds ratios were estimated by multivariable logistic regression models.

Interventions—None

Key Results—Pre-admission 25(OH)D deficiency is predictive for short term and long term mortality. 30 days following ICU admission, patients with 25(OH)D deficiency have an OR for mortality of 1.69(95%CI, 1.28–2.23;P<.0001) relative to patients with 25(OH)D sufficiency. 25(OH)D deficiency remains a significant predictor of mortality at 30 days following ICU admission following multivariable adjustment (adjusted OR 1.69; 95%CI, 1.26–2.26;P<.0001). 30 days following ICU admission, patients with 25(OH)D insufficiency have an OR of 1.32(95%CI, 1.02–1.72; P=0.036) and an adjusted OR of 1.36(95%CI, 1.03–1.79;P=0.029) relative to patients with 25(OH)D sufficiency. Results were similar at 90 and 365 days following ICU admission and for in hospital mortality. In a subgroup analysis of patients who had blood cultures drawn (n=1,160), 25(OH)D deficiency was associated with increased risk of blood culture positivity. Patients with 25(OH)D insufficiency have an OR for blood culture positivity of 1.64(95%CI, 1.05–2.55;P=0.03) relative to patients with 25(OH)D sufficiency which remains significant following multivariable adjustment: OR 1.58(95%CI, 1.01–2.49;P=0.048).

Conclusion—Deficiency of 25(OH)D prior to hospital admission is a significant predictor of short and long term all cause patient mortality and blood culture positivity in a critically ill patient population.

Introduction

Vitamin D, or cholecalciferol, is primarily a product of ultraviolet light conversion of 7-dehydrocholesterol in the skin, but also from food intake, such as eggs, fish, butter, fortified milk products, and vitamin D-containing supplements. Although the role of vitamin D is to augment calcium absorption from the small intestine(1) vitamin D may influence hypertension, diabetes, cardiovascular disease, cancer, autoimmune disorders and overall mortality. (2–5) Although vitamin D deficiency has been widely implicated as an etiologic factor in a variety of chronic illnesses, and hypocalcemia has been demonstrated to strongly correlate with both APACHE (Acute Physiology and Chronic Health Evaluation) II score and patient mortality in the ICU (Intensive Care Unit)(6), the potential role of hypovitaminosis D has rarely been considered or treated in critically ill patients.

The prevalence of vitamin D deficiency and its significance in the intensive care unit (ICU) are unknown. In a recent small prospective study, 17% of the ICU patients studied had undetectable levels of vitamin D.(7) Very low serum concentrations of 25 hydroxy vitamin D (25(OH)D) and of 1,25 dihydroxyvitamin D3 (1,25(OH)$_2$D) have been documented in critically ill patients who have prolonged ICU stays likely related to immobility and lack of sun exposure.(8–12)

Whether the degree of vitamin D deficiency affects ICU survival is unknown. Vitamin D has pleiotropic effects on immunity, endothelial and mucosal functions, and glucose and calcium metabolism. Potential broad-ranging effects of vitamin D may be consistent with the observation of the vitamin D receptor in several cell types and organs, the autocrine or paracrine production of 1,25(OH)$_2$D in several extrarenal organs, and kidney endocrine production of 1,25(OH)$_2$D.(13)

Because these observations suggest that vitamin D deficiency may play a key role in outcome of critically ill patients, we performed an 11 year multicenter observational study of critically ill patients among whom 25(OH)D was measured within one year prior to hospitalization. The aim of this study is to determine the relationship between pre-admission 25(OH)D deficiency and mortality following ICU admission.

Materials and Methods

Source Population

We extracted administrative and laboratory data from individuals admitted to 2 academic teaching hospitals in Boston, Massachusetts. Brigham and Women's Hospital (BWH) is a 777-bed teaching hospital with 100 ICU beds. Massachusetts General Hospital (MGH) is a 902-bed teaching hospital with 109 ICU beds. The two hospitals provide primary as well as tertiary care to an ethnically and socioeconomically diverse population within eastern Massachusetts and the surrounding region.

Data Sources

Data on all patients admitted to BWH or MGH between November 2, 1997 and April 1, 2009 were obtained through a computerized registry which serves as a central clinical data warehouse for all inpatients and outpatients seen at these hospitals. The database contains information on demographics, medications, laboratory values, microbiology data, procedures and the records of inpatient and outpatients. Approval for the study was granted by the Institutional Review Board of BWH and MGH. The Institutional Review Board waived the need for informed consent

The following data were retrieved: Demographics, Vital status for up to 11 years following ICU admission, pre-admission 25(OH)D measured between 7 and 365 days of hospital admission, year and season 25(OH)D was measured, microbiology data, latitude of patient address, Hospital admission and discharge date, Diagnosis Related Group (DRG) assigned at discharge, International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9CM) codes, and Current Procedural Terminology (CPT) codes for in-hospital procedures. The primary analyses examined the pre-admission 25(OH)D in patients as the exposure of interest.

Study Population

During the 11-year period of study there were 54,392 unique patients, age 18 years, who were assigned the CPT code 99291 (critical care, first 30–74 minutes). 205 foreign patients without Social Security Numbers were identified and excluded as vital status in this study is determined by the Social Security Death Index. We excluded 2,372 patients assigned CPT code 99291 who received care only in the Emergency Room, were not admitted and were not assigned a DRG. In patients with multiple ICU admissions the first date of CPT code 99291 assignment was used. 51,815 patients constituted the total ICU population.

A total of 2,439 patients in the total ICU population had 25(OH)D drawn 7 to 365 days prior to the first day of CPT code 99291 assignment. 36 of the 2,435 patients who received vitamin D supplementation following the 25(OH)D level draw date were identified and excluded. 2,399 patients constituted the study cohort.

Exposure of Interest and Comorbidities

The exposure of interest was pre-admission 25(OH)D and categorized a priori as deficiency (25(OH)D 15 ng/mL), insufficiency (25(OH)D 16–29 ng/mL) and sufficiency (25(OH)D 30 ng/mL).(14)

We utilized the Deyo-Charlson index to assess the burden of chronic illness.(15) The Deyo-Charlson index consists of 17 co-morbidities, which are weighted and summed to produce a score each with an associated weight based on the adjusted risk of one-year mortality. This score ranges from 0 to 33, with higher scores indicating a higher burden. The score does not measure type or severity of acute illness.(15–16) We employed the ICD-9 coding algorithms

developed by Quan et al(17) to derive a co-morbidity score for each patient. The validity of the algorithms by Quan et al for ICD-9 coding from administrative data is reported.(17) Due to scant representation, Deyo-Charlson index scores   8 were combined.

Patient Type is defined as Medical or Surgical and incorporates the Diagnostic Related Grouping (DRG) methodology, devised by Centers for Medicare & Medicaid Services (CMS).(18)

Sepsis was defined by the presence of any of the following ICD-9-CM codes during hospitalization: 038.0–038.9, 020.0, 790.7, 117.9, 112.5, 112.81. (19) Acute Myocardial Infarct is defined by ICD-9-CM 410.0–410.9(20) assignment prior to or on day of ICU admission. Number of organs with failure was adapted from Martin et al(19) and defined by a combination of ICD-9-CM and CPT codes relating to acute organ dysfunction assigned from 3 days prior to ICU admission to 30 days after ICU admission, as outlined in the Supplemental Digital Content.

Procedures were determined by CPT codes as follows: CABG surgery performed on the day prior or after ICU admission (CPT codes 33510 to 33536). Percutaneous Coronary Intervention including stents on the day prior or after ICU admission (CPT codes 92980 to 92984, 92995, 92996, 93508, 93510 to 93529, 93539 to 93540, 93543, and 93545 to 93552). (21) Renal Replacement Therapy in the ICU (Hemodialysis code: CPT 90935; Continuous Renal Replacement Therapy code: CPT 90945)

All patients who had blood cultures drawn 48 hours prior or subsequent to an ICU admission were identified. Blood cultures were defined as positive if aerobic, anaerobic or fungal blood cultures grew identifiable organisms.

Assessment of Mortality

Information on vital status for the study cohort was obtained from the Social Security Death Index. The Social Security Death Index yields a high sensitivity and specificity for classifying deaths.(22–23) The censoring date was April 2, 2010.

End Points

The primary end point was 30 day mortality following ICU admission. Pre-specified secondary end points included 90 day, 365 day and in-hospital morality.

Statistical Analysis

Categorical covariates were described by frequency distribution, and compared across vitamin D groups using contingency tables and chi-square testing. Continuous covariates were examined graphically (e.g., histogram, box plot) and in terms of summary statistics (mean, SD, median, inter-quartile range), and compared across exposure groups using one-way ANOVA. The outcomes considered were death by days 30, 90 and 365 post-ICU admission, in hospital mortality and blood culture positivity.

Unadjusted associations between vitamin D groups and outcomes were estimated by Mantel Haenszel methods and by bivariable logistic regression analysis. Adjusted odds ratios were estimated by multivariable logistic regression models with inclusion of covariate terms thought to plausibly interact with both vitamin D levels and mortality. For the primary model (30-day mortality), specification of each continuous covariate (as a linear versus categorical term) was adjudicated by the empiric association with the primary outcome using Akaike's Information Criterion; overall model fit was assessed using the Hosmer Lemeshow test. Models for secondary analyses (90-day, 365-day and in-hospital mortality)

were specified identically to the primary model in order to bear greatest analogy. Sensitivity analysis were performed for patients with 25(OH)D measured < 60 days (n=1011) or measured < 90 days (n=1236) prior to hospital admission. All p-values presented are two-tailed; values below 0.05 were considered nominally significant. All analyses are performed using STATA 10.0MP (College Station, TX).

Results

Table 1 shows demographic characteristics of the study population. The majority of patients were women (57.2%), white (80.3%) and had medical related DRGs (58.3%). 41.7% of patients had surgical related DRGs. The mean age at ICU admission was 64.9 (SD 16.6) years. The mean Latitude was 42.2 (SD 1.4) degrees North. The mean 25(OH)D was 26.4 (SD 15.2) ng/mL. The majority of vitamin D measurements occurred 3 months prior to ICU admission (29.8% within 1 month, 51.6% within 3 months and 73.3% within 6 months).

Based upon ICD-9-CM code criteria, 287 patients were identified with acute myocardial infarct and 577 patients were identified with sepsis and 143 of patients had positive blood cultures. In the study cohort, procedures included CABG surgery in 9, Percutaneous Coronary Intervention in 19 and Renal Replacement Therapy in 22. Due to scant representation, procedures were not further analyzed in the cohort.

The study cohort differs from the total ICU population in the period studied. In general, the study cohort is an older predominately female group with higher disease comorbidity, more sepsis by ICD-9 criteria, less organ failure, less blood culture positivity and a higher mortality than the total ICU population (Table 1).

Patient characteristics of the study cohort were stratified according to preadmission 25(OH)D levels (Table 2). Factors that significantly differed between stratified groups included age, race, season, sepsis and number of organs with failure. Factors that did not significantly differ between stratified groups included gender, blood culture positivity, Deyo-Charlson Index, Latitude, Neighborhood Poverty, type (surgical vs medical) and acute myocardial infarction. Due to overlap of ICD-9 codes with the Deyo-Charlson Index, the number of organs with failure variable was not further analyzed in the cohort.

Primary Outcome

Pre-admission 25(OH)D was a strong predictor of all cause mortality with a significant risk gradient across 25(OH)D groups (Table 3). The risk of mortality 30 days following ICU admission was 1.3- and 1.7-fold higher in patients with 25(OH)D values in the insufficient and deficient groups, respectively, compared with those with vitamin D sufficiency. 25(OH)D in the cohort remains a significant predictor of risk of mortality following adjustment for age, sex, race, Deyo-Charlson index, season, type (surgical vs medical) and sepsis. The adjusted risk of mortality was 1.4- and 1.7-fold higher in patients with 25(OH)D values in the insufficient and deficient groups, respectively, compared with those with vitamin D sufficiency. (Table 3)

Secondary Outcomes

The risk of mortality 90 days following ICU admission was 1.4- and 1.6-fold higher in patients with 25(OH)D values in the insufficient and deficient groups, respectively, compared with those with vitamin D sufficiency. The multivariable adjusted risk of mortality was 1.5- and 1.7-fold higher in patients with 25(OH)D values in the insufficient and deficient groups, respectively, compared with those with vitamin D sufficiency. (Table 3)

The risk of mortality 365 days following ICU admission was 1.4- and 1.6-fold higher in patients with 25(OH)D values in the insufficient and deficient groups, respectively, compared with those with vitamin D sufficiency. The multivariable adjusted risk of mortality was 1.3- and 1.4-fold higher in patients with 25(OH)D values in the insufficient and deficient groups, respectively, compared with those with vitamin D sufficiency. (Table 3)

The risk of in-hospital mortality following ICU admission was 1.3- and 1.8-fold higher in patients with 25(OH)D values in the insufficient and deficient groups, respectively, compared with those with vitamin D sufficiency. The multivariable adjusted risk of mortality was 1.3- and 1.7-fold higher in patients with 25(OH)D values in the insufficient and deficient groups, respectively, compared with those with vitamin D sufficiency. (Table 3)

The association between vitamin D and mortality was not materially modified with additional covariate adjustment for number of failed organs (data not shown). The association between vitamin D and mortality was not modified by the presence or absence of sepsis (P-interaction: 30 day = 0.72, 90 day = 0.32, 365 day = 0.32, in-hospital = 0.84). The interaction tests suggests that the association between 25(OH)D level and mortality is the same in septic patients as in non-septic patients.

A sensitivity analysis was performed of the effects of excluding patients with pre-admission 25(OH)D levels obtained >90 days prior to admission. Following exclusion of such patients, the association between vitamin D and in-hospital, 30 day, 90 day or 365 day mortality following critical care was not modified. Additionally, sensitivity analysis of the effects of excluding patients with preadmission 25(OH)D levels obtained >60 days prior to admission does not materially change the association between vitamin D and mortality.(Table 4)

In a subgroup analysis of patients who had blood cultures drawn (n=1,160), pre-admission 25(OH)D deficiency was associated with increased risk of blood culture positivity. (Table 5) The risk for blood culture positivity of mortality was 1.6-fold higher in patients with 25(OH)D values in the deficient group, compared with those with vitamin D sufficiency. The multivariable adjusted risk for blood culture positivity was 1.6-fold higher in patients with 25(OH)D values in the deficient group, compared with those with vitamin D sufficiency. Patients with 25(OH)D insufficiency (15–30 ng/mL) show no significant difference in risk of blood culture positivity relative to patients with vitamin D sufficiency.

Discussion

The present study aimed to determine whether pre-admission 25(OH)D was associated with all cause mortality following ICU admission. This large 11-year multicenter observational study illustrates the all cause mortality risk of pre-admission 25(OH)D deficiency. Pre-admission 25(OH)D deficiency was a significant predictor of 30, 90, 365 post ICU day mortality as well as in-hospital mortality and remained a significant predictor of survival following multivariable adjustments for relevant comorbidities. In addition, our subset analysis suggests an increased susceptibility to blood culture positivity in patients with vitamin D deficiency.

The mechanism for increased mortality following ICU admission in patients with hypovitaminosis D may be related to the pleiotropic functions of vitamin D. Vitamin D inhibits vascular smooth-muscle cell proliferation,(24) protects normal endotheilial function, (25) and modulates inflammatory processes.(26–27)

Although $1,25(OH)_2D$ primarily has inhibitory effects on the adaptive immune response, some of its effects on innate immune cells are stimulatory. Studies provide evidence for defects in macrophage functions, such as chemotaxis, phagocytosis and the production of proinflammatory cytokines, in vitamin D deficient conditions.(28) Vitamin D is a key link between Toll Like Receptor (TLR) activation and antibacterial responses in innate immunity.(29) TLR stimulation of human macrophages induces conversion of 25(OH)D to active 1,25(OH)2D; expression of the vitamin D receptor; and, production of cathelicidin a downstream target of the vitamin D receptor capable of promoting innate immunity.(30–32)

Our data is consistent with an analysis of the NHANES (National Health and Nutrition Examination Survey) data in which low vitamin D levels were associated with an increased incidence of upper respiratory tract infections.(33) In another study, patients with severe vitamin D deficiency were abnormally susceptible to infections such as tuberculosis(34) and infection in general.(35–36) Similarly, in a Meta-analysis of 18 trials involving 57,311 randomly assigned subjects, Autier found that vitamin D supplementation reduced all-cause mortality by 7% (CI, 1% to 13%).(5) These observations and others suggest that hypovitaminosis D is likely to play a key role in infection, and cardiac and metabolic dysfunctions in critically ill patients.

The present study has limitations. Selection bias may exist as the patient cohort under study had their vitamin D status investigated for a particular reason that may be absent in other patients treated with critical care. This is demonstrated by the significant differences in the total ICU population and the 25(OH)D cohort (Table 1). These noted differences may decrease the generalizability of our results to all critically ill patients. We cannot exclude the possibility that other unmeasured variables influence mortality independently of vitamin D, which may have biased estimates. Despite adjustment for multiple potential confounders, there may be residual confounding variables leading to observed differences in outcomes.

In a prior study of an outpatient population, the intra-person Pearson correlation coefficient for 25(OH)D is demonstrated to be 0.70 at three years between blood draws following adjustments for age, race, and season.(37) The majority of our cohort had 25(OH)D levels drawn 3 months prior to ICU admission. Our sensitivity analysis demonstrates preservation of the observed vitamin D-mortality association with less than 90 days between 25(OH)D level and ICU admission. Despite this observation, vitamin D levels at the time of critical care initiation are not available in this cohort and may have changed since pre-admission values were determined. We do not have data available on over the counter supplementation or vitamin D prescribed by providers outside of clinics related to the hospitals under study. Such supplementation may have altered the true 25(OH)D-mortality association.

We define sepsis and comorbidity based on administrative ICD-9-CM coding. Administrative coding has been evaluated for particular disease states(38–42) and comorbidity profiles.(43–44) The accuracy of ICD-9-CM coding for the identification of medical conditions remains controversial.(19) The several steps and participants required to assign ICD-9-CM codes introduce potential for error.(45) Despite these shortcomings, the ICD-9-CM code 038.x is reported to have a high positive predictive value for the identification of true cases of sepsis(46), and a high sensitivity(47), specificity(19) and negative predictive value.(19) Algorithms developed to recode ICD-9-CM coded data into a Deyo-Charlson index are well studied, validated and well suited for use in administrative datasets.(48–49)

Our finding that pre-admission 25(OH)D is a significant predictor of mortality does not include physiologic data. In the administrative database used in this study, temperature, blood pressure, heart rate, respiratory rate and Glasgow Coma scale data is not available and

thus APACHE scores are absent. Scoring systems inclusive of physiological data including APACHE are strong predictors of mortality in ICU patients.(50) Further, it is not known if illness severity influences vitamin D levels at time of ICU admission. It is possible that inclusion of a physiologic score in the analysis may materially alter the 25(OH)D-mortality association. With the addition of age and gender data, the Deyo-Charlson comorbidity index can be considered an alternative method of risk adjustment in the absence of physiologic data.(51) However, despite multivariable adjustment the absence of physiologic data remains a limitation of our study. Finally, we are also unable to adjust for body mass index, immobilization, lack of sun exposure and smoking status, factors that can alter 25(OH)D.

The present study has several strengths. As other chronic medical conditions may affect the attributed cause of death, all-cause mortality is considered an unbiased and clinically relevant outcome in long-term observational studies.(52–53) Utilization of the Social Security Death Index allows for long term follow up of the cohort following hospital discharge. Our study is a relatively large regional multicenter study with sufficient numbers of patients to ensure the adequate reliability of our mortality estimates (N=2,399, hospital mortality rate =15.6%). We employed previous records to define comorbidities which increase prevalence of these conditions, resulting in a better risk adjustment.(40, 54) Measurements of 25(OH)D prior to ICU admission allow for the inference of the potential importance of vitamin D sufficiency prior to the onset of critical illness.

In aggregate, these data demonstrate that pre-admission 25(OH)D deficiency is strongly associated with the risk of death in critical illness and that this risk is independent of other risk factors. In addition, in patients with blood cultures drawn, 25(OH)D deficiency is strongly associated with the risk of blood culture positivity. In concert with the basic science evidence, we believe that these results provide clinical evidence of a potential link between vitamin D and outcomes of critical illness. However, studies of this relationship in a cohort with uniform methods for the measurement of vitamin D and a uniform timing of measurement relative to the onset of critical illness are clearly warranted to further elucidate the role of vitamin D in critical illness. Positive findings in prospective studies may establish 25(OH)D as an important and modifiable risk factor for ICU mortality. Given the safety profile of vitamin D, positive results would provide strong motivation for examining the utility of activated vitamin D as a novel therapeutic agent designed to improve survival in critical illness.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Patient Characteristics of the Study Population

	Study Cohort	Total ICU Population	P
N	2,399	51,815	
Gender-no.(%)			0.03
Female	1,369 (57.0)	21,671 (41.8)	
Male	1,030 (43.0)	30,144 (58.2)	
Race-no.(%)			
African American	195 (8.1)	3,350 (6.5)	0.001
Asian	58 (2.4)	954 (1.8)	0.04
Hispanic	117 (4.9)	2,558 (4.9)	0.9
Not Recorded	81 (3.4)	2,643 (5.1)	0.0002
Other	21 (0.8)	1075 (2.1)	<.0001
White	1,927 (80.3)	41,235 (79.6)	0.4
Age at ICU admission mean (SD)	64.9 (16.6)	61.69 (18.4)	<.0001
Latitude mean (SD)	42.2 (1.4)	42.2 (1.6)	1.0
Deyo-Charlson Index mean (SD)	5.6 (3.4)	3.0 (2.1)	<.0001
25(OH)D mean (SD)	26.4 (15.2)	-- --	
Patient Type-no.(%)			<.0001
Medical	1,399 (58.3)	26,221 (50.6)	
Surgical	1,000 (41.7)	25,596 (49.4)	
ICU events-no.(%)			
Acute Myocardial Infarct	287 (12.0)	7,981 (15.4)	<.0001
Sepsis	577 (24.1)	7,012 (13.5)	<.0001
CABG	9 (0.4)	2,822 (5.4)	<.0001
Mortality Rates %			
30-day	16.7	14.2	0.0006
90-day	23.2	18.7	<.0001
365-day	32.2	26.3	<.0001
In-hospital	15.6	13.0	0.0002
No. of organs with failure – no.(%)			<.0001
0	1405 (57.0)	20,067 (38.7)	
1	468 (19.0)	17,731 (34.2)	
2	294 (11.9)	8,654 (16.7)	
3	296 (12.0)	5,363 (10.4)	
Blood Culture Positivity – no.(%)	143 (12.3)	3070 (16.5)	0.0001

Table 2

Stratified Patient Characteristics of the 25(OH)D Cohort

| | Pre-admission 25(OH)D | | | |
	15 ng/mL	15–30 ng/mL	30 ng/mL	P-value
N	637	918	844	
Age-mean(SD)	61.9 (16.9)	65.1 (16.5)	67.0 (16.2)	<.0001
Gender-no.(%)				0.07
Female	352 (55.3)	511 (55.7)	509 (60.3)	
Male	285 (44.7)	407 (44.3)	335 (39.7)	
Race-no.(%)				<.0001
White	467 (73.2)	753 (81.2)	706 (83.8)	
Non-White	170 (26.7)	165 (18.0)	138 (16.4)	
Patient Type-no.(%)				0.4
Medical	382 (60.0)	520 (56.6)	497 (58.9)	
Surgical	255 (40.0)	398 (43.4)	347 (41.1)	
Season 25(OH)D drawn-no.(%)				0.005
Summer	143 (22.5)	218 (23.8)	227 (26.9)	
Winter	153 (24.0)	216 (23.5)	175 (20.7)	
Fall	136 (21.4)	222 (24.2)	233 (27.6)	
Spring	205 (32.2)	262 (28.5)	209 (24.8)	
Deyo-Charlson Index-no.(%)				0.1
0	15 (2.4)	18 (2.0)	21 (2.5)	
1	24 (3.8)	59 (6.4)	37 (4.4)	
2	67 (10.5)	90 (9.8)	70 (8.3)	
3	88 (13.8)	111 (12.1)	103 (12.2)	
4	77 (12.1)	121 (13.2)	102 (12.1)	
5	81 (12.7)	130 (14.2)	111 (13.2)	
6	72 (11.3)	112 (12.2)	97 (11.5)	
7	64 (10.1)	66 (7.2)	63 (7.5)	
8	149 (23.4)	211 (23.0)	240 (28.4)	
Sepsis-no.(%)	193 (30.3)	220 (24.0)	164 (19.4)	<.0001
No. of organs with failure-no.(%)				<.0001
0	311 (49.0)	477 (52.0)	555 (65.8)	
1	134 (21.1)	199 (21.7)	133 (15.8)	
2	100 (15.6)	119 (13.0)	75 (8.9)	
3	92 (14.4)	123 (13.4)	81 (9.6)	
Blood Culture Positivity-no.(%)	53 (15.7)	50 (11.1)	39 (10.3)	0.06
Acute Myocardial Infarct-no.(%)	68 (10.7)	112 (12.2)	106 (12.6)	0.5

Table 3

Unadjusted and Adjusted Associations between Pre-admission 25(OH)D level and outcomes

	OR	95% CI	P
Unadjusted			
30-day mortality			
25(OH)D 15 ng/m L	1.69	1.28–2.23	<.0001
25(OH)D 15–30 ng/mL	1.32	1.02–1.72	0.036
25(OH)D 30 ng/mL	1.00		
90-day mortality			
25(OH)D 15 ng/m L	1.61	1.26–2.05	<.0001
25(OH)D 15–30 ng/mL	1.41	1.13–1.78	0.003
25(OH)D 30 ng/mL	1.00		
365-day mortality			
25(OH)D 15 ng/m L	1.56	1.25–1.95	<.0001
25(OH)D 15–30 ng/mL	1.32	1.08–1.62	0.008
25(OH)D 30 ng/mL	1.00		
In-hospital mortality			
25(OH)D <=15 ng/mL	1.77	1.34–2.36	<.0001
25(OH)D 15–30 ng/mL	1.34	1.02–1.76	0.036
25(OH)D 30 ng/mL	1.00		
Adjusted			
30-day mortality			
25(OH)D 15 ng/m L	1.69	1.26–2.26	<.0001
25(OH)D 15–30 ng/mL	1.36	1.03–1.79	0.029
25(OH)D 30 ng/mL	1.00		
90-day mortality			
25(OH)D 15 ng/m L	1.67	1.28–2.17	<.0001
25(OH)D 15–30 ng/mL	1.51	1.19–1.93	0.001
25(OH)D 30 ng/mL	1.00		
365-day mortality			
25(OH)D 15 ng/m L	1.72	1.35–2.19	<.0001
25(OH)D 15–30 ng/mL	1.44	1.15–1.79	0.001
25(OH)D 30 ng/mL	1.00		
In-hospital mortality			
25(OH)D 15 ng/m L	1.72	1.27–2.33	<.0001
25(OH)D 15–30 ng/mL	1.34	1.01–1.79	0.04
25(OH)D 30 ng/mL	1.00		

Note: Referent in each case is 25(OH)D 30 ng/mL. Estimates adjusted for age, gender, race (white, non-white), Deyo-Charlson index, season, type (surgical vs medical) and sepsis.

Table 4

Sensitivity Analysis of days between 25(OH)D measurement and hospital admission

	>90 days excluded (n=1236)			>60 days excluded (n=1011)		
	OR	95%CI	P	OR	95%CI	P
Unadjusted						
30-day mortality						
25(OH)D <15 ng/mL	1.92	1.34–2.75	<.0001	1.90	1.27–2.82	0.002
25(OH)D 15–30 ng/mL	1.26	0.87–1.81	0.2	1.21	0.80–1.81	0.4
25(OH)D 30 ng/mL	1.0	1.0–1.0		1.0	1.0–1.0	
90-day mortality						
25(OH)D 15 ng/m L	1.71	1.24–2.38	0.001	1.74	1.21–2.49	0.003
25(OH)D 15–30 ng/mL	1.39	1.01–1.92	0.04	1.34	0.93–1.91	0.1
25(OH)D 30 ng/mL	1.0	1.0–1.0		1.0	1.0–1.0	
365-day mortality						
25(OH)D 15 ng/mL	1.83	1.35–2.47	<.0001	1.81	1.30–2.52	<.0001
25(OH)D 15–30 ng/mL	1.50	1.12–2.00	0.007	1.41	1.02–1.96	0.04
25(OH)D 30 ng/mL	1.0	1.0–1.0		1.0	1.0–1.0	
In-hospital mortality						
25(OH)D 15 ng/m L	1.90	1.32–2.75	0.001	1.86	1.24–2.78	0.003
25(OH)D 15–30 ng/mL	1.32	0.91–1.91	0.1	1.28	0.85–1.92	0.2
25(OH)D 30 ng/mL	1.0	1.0–1.0		1.0	1.0–1.0	
Adjusted						
30-day mortality						
25(OH)D 15 ng/m L	1.91	1.30–2.81	0.001	1.77	1.16–2.71	0.009
25(OH)D 15–30 ng/mL	1.46	1.04–2.05	0.03	1.24	0.81–1.90	0.3
25(OH)D 30 ng/mL	1.0	1.0–1.0		1.0	1.0–1.0	
90-day mortality						
25(OH)D 15 ng/mL	1.72	1.20–2.46	0.003	1.64	1.21–2.49	0.01
25(OH)D 15–30 ng/mL	1.46	1.04–2.05	0.03	1.42	0.97–2.09	0.07
25(OH)D 30 ng/mL	1.0	1.0–1.0		1.0	1.0–1.0	
365-day mortality						
25(OH)D 15 ng/m L	2.00	1.43–2.79	<.0001	1.87	1.29–2.69	0.001

	>90 days excluded (n=1236)			>60 days excluded (n=1011)		
	OR	95%CI	P	OR	95%CI	P
25(OH)D 15–30 ng/mL	1.62	1.18–2.22	0.003	1.54	1.09–2.19	0.02
25(OH)D 30 ng/mL	1.0	1.0–1.0		1.0	1.0–1.0	
In-hospital mortality						
25(OH)D 15 ng/m L	1.76	1.18–2.62	0.006	1.62	1.05–2.51	0.03
25(OH)D 15–30 ng/mL	1.27	0.86–1.88	0.2	1.28	0.83–1.97	0.3
25(OH)D 30 ng/mL	1.0	1.0–1.0		1.0	1.0–1.0	

Note: Referent in each case is 25(OH)D 30 ng/mL. Estimates adjusted for age, gender, race (white, non-white), Deyo-Charlson index, season, type (surgical vs medical) and sepsis.

Table 5

Unadjusted and Adjusted associations between Pre-admission 25(OH)D level and blood culture positivity

	OR	95% CI	P
Unadjusted			
25(OH)D 15 ng/m L	1.64	1.05–2.55	0.028
25(OH)D 15–30 ng/mL	1.08	0.70–1.69	0.72
25(OH)D 30 ng/mL	1.00		
Adjusted			
25(OH)D 15 ng/m L	1.58	1.01–2.49	0.048
25(OH)D 15–30 ng/mL	1.02	0.65–1.59	0.9
25(OH)D 30 ng/mL	1.00		

Note: Referent in each case is 25(OH)D   30 ng/mL. Estimates adjusted for age, gender, race (white, non-white), and Deyo-Charlson index.