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Original article

Increases in pre-hospitalization serum 25(OH)D concentrations are associated with improved 30-day mortality after hospital admission: A cohort study

Karin Amrein [a], Augusto A. Litonjua [b], Takuhiro Moromizato [c], Sadeq A. Quraishi [d], Fiona K. Gibbons [e], Thomas R. Pieber [a], Carlos A. Camargo Jr. [f], Edward Giovannucci [g], Kenneth B. Christopher [h, *]

[a] Department of Internal Medicine, Division of Endocrinology and Metabolism, Medical University of Graz, Austria
[b] Channing Division of Network Medicine and Pulmonary and Critical Care Division, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA
[c] Department of Medicine, Okinawa Hokubu Prefectural Hospital, Okinawa, Japan
[d] Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, USA
[e] Pulmonary and Critical Care Medicine, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA
[f] Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA, USA
[g] Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA, USA
[h] The Nathan E. Hellman Memorial Laboratory, Renal Division, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

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SUMMARY

Context: Pre-hospital vitamin D status may be a modifiable risk factor for all-cause mortality among hospitalized patients.
Objective: To examine the association between increases in serum 25-hydroxyvitamin D [25(OH)D] levels during the year before hospitalization and risk of 30-day all-cause mortality after hospital admission.
Design: Retrospective cohort study.
Setting: Two Boston teaching hospitals.
Patients or other participants: We studied 4344 adults hospitalized between 1993 and 2011 who had serum 25(OH)D concentrations measured at least twice within 7–365 days before the index hospitalization.
Intervention(s): None.
Main outcome measure(s): The exposure of interest was change in pre-hospital serum 25(OH)D concentrations. The main outcome was 30-day all-cause mortality. We used mixed-effects logistic regression to describe how 30-day mortality differed with changes in pre-hospital 25(OH)D concentrations. Additionally, the odds of 30-day mortality in patients with pre-hospital 25(OH)D increases of ≥10 ng/mL was compared to that of patients with increases of <10 ng/mL.
Results: In a mixed-effect logistic regression model adjusted for age, gender, race, type (medical/surgical), Deyo-Charlson Index, creatinine and hematocrit, 30-day all-cause mortality rate was 8% (95%CI: 1–15) lower for each 10 ng/mL increase in pre-hospital 25(OH)D ($P = 0.025$) compared with the 30-day all-cause mortality rate in the entire cohort. In an adjusted logistic regression model, absolute changes of ≥10 ng/mL in patients with initial 25(OH)D concentrations < 20 ng/mL (n = 1944) decreased the odds of 30-day all-cause mortality by 48% (adjusted OR 0.52; 95%CI 0.30–0.93; $P = 0.026$) compared to patients with changes of <10 ng/mL.

* Corresponding author. Renal Division, Department of Medicine, Brigham and Women's Hospital, 75 Francis Street, MRB 418, Boston, MA 02115, USA. Tel.: +1 617 272 0535; fax: +1 617 732 6392.
E-mail address: kbchristopher@partners.org (K.B. Christopher).

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Conclusions: In patients with initial 25(OH)D < 20 ng/mL, subsequent improvements in vitamin D status before hospitalization are associated with decreased odds of 30-day all-cause mortality after hospital admission. A causal relation may not be inferred from this observational study.

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1. Introduction

Epidemiologic studies consistently show that low vitamin D status is prevalent throughout the world [1]. Serum 25-hydroxyvitamin D [25(OH)D] concentrations are the most widely recognized marker of overall vitamin D status [2], and mortality risk appears to decrease as serum 25(OH)D increase [3]. Studies in hospitalized patients suggest a relationship between vitamin D status and important outcomes [4,5] and indicate that serum 25(OH)D concentrations < 20 ng/mL are associated with adverse outcomes [6–8].

Interventional trials have shown anti-inflammatory and immune modulating effects related to vitamin D supplementation [9–11]. However, benefit in studies of vitamin D supplementation is not universal [12–15] and the use of annual high-dose, cholecalciferol (vitamin D3) therapy is shown to be associated with harm [16]. Recently, results from a hypothesis generating subgroup analysis of the VITdAL-ICU randomized controlled trial noted that in critically ill patients with low 25(OH)D concentrations, high dose vitamin D supplementation was associated with improvement in mortality [17]. While studies suggest that pre-hospital 25(OH)D concentrations may be a modifiable risk factor for healthcare-related morbidity and mortality [8,18], to date, limited information exists regarding the association between changes in pre-hospital vitamin D status and subsequent mortality following hospitalization.

We investigated whether changes in pre-hospital serum 25(OH)D concentrations are associated with the risk of 30-day all-cause mortality in hospitalized patients. We hypothesized that improvement in 25(OH)D concentrations before hospitalization would be associated with decreased mortality during the 30 days after hospital admission. To explore this hypothesis, we performed a two-center observational cohort study of 4344 adults, hospitalized for acute care between 1993 and 2011, and who had at least 2 serum 25(OH)D concentrations drawn in the year leading up to hospitalization.

2. Materials and methods

2.1. Source population and data sources

We abstracted patient-level administrative and laboratory data from two academic hospitals: Brigham and Women's Hospital (BWH), with 793 beds and Massachusetts General Hospital (MGH) with 902 beds, both in Boston, Massachusetts. The two hospitals provide primary as well as tertiary care to an urban and suburban population, as well as a diverse population within eastern Massachusetts and New England. Both BWH and MGH have 45,000–47,000 hospital admissions per year. BWH and MGH are members of Partners HealthCare, which is the largest healthcare provider in Massachusetts, USA.

Data on all patients admitted to BWH or MGH between August 3, 1993 and January 5, 2011 were obtained through the Research Patient Data Registry (RPDR) [19] which is a data warehouse for all patient records at Partners HealthCare sites. Study was granted by the Partners Human Research Committee (Institutional Review Board). Requirement for consent was waived as the data were analyzed anonymously.

2.2. Study population

During the study period, there were approximately 1.6 million patient admissions to BWH and MGH. 24,787 individual patients were ≥18 years, had serum 25(OH)D measured between 7 and 365 days before hospitalization, and were assigned a Diagnostic Related Group (DRG) classification. Exclusions included: 23 foreign patients without Social Security Numbers (required for determining vital status); 618 patients with missing laboratory data resulting in a parent cohort of 24,146 patients. To attain the analytic cohort we further excluded 19,802 patients who had only one 25(OH)D test done in the year leading to the index hospitalization. Thus, the analytic cohort was comprised of 4344 patients of which 982 patients had more than two 25(OH)D tests in the year prior to hospitalization.

2.3. Exposure of interest and covariates

The exposure of interest was the change in pre-hospital serum 25(OH)D concentration obtained 7–365 days before hospital admission. Patients were included if they had at least two 25(OH)D assessments within the 7–365 day time frame leading up to hospital admission.

Race was either self-determined or designated by a patient representative/healthcare proxy. Patient admission 'type' incorporates DRG methodology and was defined as 'Surgical' or 'Medical'. We employed the Deyo-Charlson Index to assess chronic illness comorbidity [20]. Laboratory values other than 25(OH)D were determined on the day of hospital admission. Admission to the Intensive care unit (ICU) was defined as presence of Current Procedural Terminology (CPT) code 99291 (critical care, first 30–74 min) during hospital admission [21]. Vitamin D supplementation was determined by BWH and MGH outpatient pharmacy records for cholecalciferol or ergocalciferol prescribed 7–365 days prior to hospital admission and after the initial 25(OH)D concentration.

Changes from the expected hospital length of stay (LOS) were computed as the difference between the actual LOS and the geometric mean LOS for each DRG. The geometric mean LOS is the national mean LOS for each DRG as determined by the Centers for Medicare & Medicaid Services. LOS was not determined in patients who died in hospital (n = 104) or who left the hospital against medical advice (n = 11).

2.4. 25(OH)D assays

Between 1993 and 2011, different assays were used at the two hospitals: a chemiluminescence assay, radioimmunoassay, or liquid chromatography-mass spectroscopy (LC-MS). Date and time as well as assay type of 25(OH)D were recorded. The clinical laboratories where the assays were performed are Clinical Laboratory Improvement Amendments (CLIA) certified. The 25(OH)D assays were tested for imprecision by the clinical laboratories at both

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hospitals [18]. Method corrections were not employed when institutions changed assays. In all study subjects, the intra-subject assay was the same.

2.5. End points

The primary end point was 30-day all-cause mortality after hospital admission. Secondary endpoints included 90-day all-cause mortality, changes from the expected hospital LOS, and all cause mortality in the 30 and 90 days after hospital discharge.

2.6. Assessment of mortality

Vital status was obtained from the Social Security Administration Death Master File. We have previously validated the accuracy of in-hospital and out-of-hospital mortality in the RPDR [21]. 100% of the cohort had at least 365-day follow up. The censoring date was January 5, 2012.

2.7. Power calculations and statistical analysis

Previously, in the parent cohort ($n = 24{,}787$), we studied 25(OH)D assessments closest to the date of hospitalization [8]. From these data, we assumed that 30-day mortality would be 4% higher among the current patient cohort with 25(OH)D concentrations < 20 ng/mL on repeat measure compared to those with 25(OH)D ≥ 20 ng/mL on follow-up assessment. The 20 ng/mL cut point was chosen from Institute of Medicine vitamin D insufficiency definition [22]. With an alpha error level of 5% and a power of 80%, the required sample size for our primary end point (30-day mortality) was 537 patients with a pre-hospitalization repeat 25(OH)D < 20 ng/mL and 537 patients with a pre-hospitalization repeat 25(OH)D ≥ 20 ng/mL.

We compared categorical variables across outcome groups using contingency tables and chi-square testing. Continuous variables were compared across outcome groups using one-way analysis of variance. The primary outcome was 30-day all-cause mortality. Mixed-effect logistic regression models containing both fixed and random-effects were used for analysis of the association between 25(OH)D concentration and 30-day all-cause mortality with the dates of 25(OH)D draw within individual patients as the random effect. The variables assessed for confounding included age, race, gender, patient type, Deyo-Charlson Index, hematocrit, creatinine, ICU admission, serum calcium, time between last 25(OH)D and index hospitalization, chronic kidney disease, blood urea nitrogen (BUN), white blood cell (WBC) count, season, hospital (BWH vs. MGH), first 25(OH)D concentration, 25(OH)D assay type, vitamin D supplementation, absolute change in 25(OH)D and LOS. Confounders were selected by analyzing the maximum model and then conducting backward elimination of variables with $P > 0.10$. Of these, age at hospitalization, gender, race, patient type, Deyo-Charlson Index, creatinine and hematocrit were included in the final models. The model had a fixed effect for age at hospitalization, race, gender patient type, Deyo-Charlson Index, creatinine and hematocrit; an independent covariance structure of the random effects; and gaussian-distributed random intercepts and slopes. We next utilized mixed-effect linear regression to determine the relationship between the change in 25(OH)D and hospital LOS with random effects to account for the dates of 25(OH)D draw within individual patients.

In further analyses, we examined the exposure as a binary variable describing an increase in 25(OH)D of ≥10 ng/mL during the year leading to hospitalization. We chose the ≥10 ng/mL based on studies by others that show that serum 25(OH)D levels increase by 10 ng/ml over 4 weeks for patients on daily 1000 IU vitamin D_3 [23] and our prior work showing differential outcomes with 25(OH)D levels categorized as <10 ng/mL, 10–19.9 ng/mL, 20–29.9 ng/mL, and ≥30 ng/mL [24,25]. Adjusted odds ratios were estimated by multivariable logistic regression models with inclusion of covariate terms thought to plausibly associate with both an increase in 25(OH)D of ≥10 ng/mL and 30-day mortality. For the 30-day mortality model, decision to analyze each continuous covariate as a categorical term versus a linear term was decided by the empiric association with the primary outcome using Akaike's Information Criterion; overall model fit was determined using the Hosmer Lemeshow test.

To reduce potential bias from the non-randomized assignment of an increase in 25(OH)D over the year leading up to hospitalization, we constructed propensity scores for the allocation of increased 25(OH)D. Utilizing logistic regression, propensity scores were calculated for each cohort subject to estimate the probability for the presence or absence of an increase in 25(OH)D ≥ 10 ng/mL. Covariates selected for the propensity score development included age, race, gender, patient type, Deyo-Charlson Index, calcium >10.5 mg/dl, time between last 25(OH)D and hospital admission, hematocrit, creatinine, BUN, WBC count, season of last 25(OH)D measure, hospital, season of hospital admission and chronic kidney disease. A nested case–control was performed where a case subject (with an increase in 25(OH)D ≥ 10 ng/mL) was matched 1:1 to a control subject (without an increase in 25(OH)D ≥ 10 ng/mL) on the basis of their propensity score. We utilized Mahalanobis metric matching within calipers defined by the propensity score to match the smaller cohorts.

For the time to mortality, we estimated the survival curves according to increase in 25(OH)D group with the Kaplan–Meier method and the log-rank test. Locally weighted scatter plot smoothing (LOWESS) was utilized to graphically represent the relationship between the change in 25(OH)D and 30-day mortality. In all analyses, p-values were two-tailed with values below 0.05 considered statistically significant. All analyses were performed with STATA 13.1 MP statistical software (StataCorp LP, College Station, TX).

3. Results

Patient characteristics of the study cohort were stratified according to 30-day mortality (Table 1). At hospital admission, the mean age was 61 years. There were 2737 (63%) females, 3437 (79%) white patients and 2635 (61%) had a medically-related DRG. Factors that were associated with 30-day mortality included older age, male gender, medical patient type, higher Deyo-Charlson Index, lower hematocrit, higher creatinine, BUN, higher chronic kidney disease stage, ICU admission, and longer LOS. The mean (standard deviation) final pre-hospital 25(OH)D concentration was 32.2 (SD 16.7) ng/mL. 28% of the patients were prescribed ergocalciferol or cholecalciferol following the initial 25(OH)D concentration. 14.7% of the patients received critical care services during the index hospitalization. In-hospital mortality rate was 2.4%, while 30, 90 and 365-day mortality rates were 3.1%, 6.0%, and 11.8%, respectively. Overall the analytic cohort was similar to the parent cohort of 24,146 patients (Supplemental Table 1).

3.1. Primary outcome

Mortality in the 30 days after hospital admission was lower in patients with an increase in serum 25(OH)D concentration before hospitalization. In a mixed-effect logistic regression model adjusted for age, gender, race, type, Deyo-Charlson Index, hematocrit, creatinine as well as the random-effects structure, for each 10 ng/mL increase in 25(OH)D during the year leading to hospital

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Table 1
Adjusted patient characteristics associated with 30-day all-cause mortality (n = 4344).

Patient characteristics	Bivariable models			Multivariable models	
	No.(%) alive	No.(%) expired	P-value	OR (95% CI)	P-value
Number of patients, n	4210	134			
Age (year;mean ± SD)	60.5 ± 17.1	69.5 ± 15.7	<0.001*	1.03 (1.02–1.04)	<0.001
Gender			0.002		
Female	2670 (63)	67 (50)		Reference	
Male	1540 (37)	67 (50)		1.31 (1.03–1.68)	0.030
Race			0.20		
White	3325 (79)	112 (84)		Reference	
Non-White	885 (21)	22 (16)		0.75 (0.55–1.03)	0.073
Patient type			<0.001		
Medical	2518 (60)	117 (87)		Reference	
Surgical	1692 (40)	17 (13)		0.30 (0.21–0.42)	<0.001
Deyo-Charlson index			<0.001		
0–3	1393 (33)	10 (7)		Reference	
3–6	1140 (27)	20 (15)		1.48 (0.88–2.48)	0.14
≥7	1677 (40)	104 (78)		4.80 (3.06–7.52)	<0.001
Hematocrit at Hospital Admission			0.001		
<30%	617 (15)	39 (29)		Reference	
≥30%	3593 (85)	95 (71)		0.48 (0.37–0.63)	<0.001
Creatinine at Hospital admission			<0.001		
≤0.8 mg/dl	1060 (25)	23 (17)		Reference	
0.8–1.5 mg/dl	2020 (48)	46 (34)		0.60 (0.42–0.84)	0.003
1.5–3.0 mg/dl	622 (15)	35 (26)		0.64 (0.44–0.94)	0.024
>3.0 mg/dl	508 (12)	30 (22)		1.13 (0.77–1.66)	0.54
ICU admission	572 (14)	67 (50)	<0.001	Not included in multivariable models	
Serum calcium			0.38	Not included in multivariable models	
≤10.5 mg/dl	3695 (88)	121 (90)			
>10.5 mg/dl	515 (12)	13 (10)			
Time between final 25(OH)D and index hospitalization[b]			0.59	Not included in multivariable models	
>90 days	1606 (38)	48 (36)			
≤90 days	2604 (62)	86 (64)			
Chronic kidney disease stage			<0.001	Not included in multivariable models	
0–2	2260 (55)	43 (32)			
3	1133 (28)	42 (31)			
4	393 (10)	23 (17)			
5	323 (8)	26 (19)			
Blood urea nitrogen at hospital admission			<0.001	Not included in multivariable models	
<10 mg/dl	794 (19)	11 (8)			
10–19 mg/dl	1633 (39)	30 (22)			
20–39 mg/dl	1086 (26)	48 (36)			
≥40 mg/dl	697 (17)	45 (34)			
White blood cell count at hospital admission			0.190	Not included in multivariable models	
$<4 \times 10^3/\mu L$	137 (3)	6 (4)			
$4–10 \times 10^3/\mu L$	1929 (46)	45 (34)			
$\geq 10 \times 10^3/\mu L$	2144 (51)	83 (62)			
Season[a]			0.76	Not included in multivariable models	
Winter	957 (23)	32 (24)			
Spring	1120 (27)	37 (28)			
Summer	1016 (24)	35 (26)			
Fall	1117 (27)	30 (22)			
Hospital			0.80	Not included in multivariable models	
MGH	2903 (69)	91 (68)			
BWH	1307 (31)	43 (32)			
First 25(OH)D (mean ± SD)	24.9 ± 15.0	24.0 ± 15.1	0.48*	Not included in multivariable models	
25(OH)D Assay			0.010	Not included in multivariable models	
Radio-immuno assay	790 (19)	32 (24)			
Chemiluminescence assay	1135 (27)	47 (35)			
Mass spectrometry	2285 (54)	55 (41)			
Vitamin D supplementation	1189 (28)	33 (25)	0.36	Not included in multivariable models	
Delta 25(OH)D (per 10 ng/mL; mean ± SD)	2.49 ± 1.5	2.41 ± 1.5	0.51*	0.91 (0.85–0.99)	0.025
Length of Stay (mean ± SD)	6.1 ± 8.6	9.1 ± 8.3	<0.001*	Not included in multivariable models	

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
Bivariable Model P values determined by chi-square unless designated by (*) then the P value was determined by Kruskal Wallis.
Multivariable Model P values are from mixed-effects regression models with 25(OH)D sample date-specific random intercepts.
Variables in bivariable analysis that were not also in multivariable analysis either did not meet criteria for inclusion in the multivariable model, or did alter model.
Fit and were not important confounders.
[a] Season of 25(OH)D measured closest to hospital admission.
[b] Days between final 25(OH)D concentration and index hospitalization date.

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admission was associated with a relative decrease of 8.4% in the 30-day mortality rate (OR 0.92, 95% CI 0.85–0.99; $P = 0.028$) (Table 1). When cohort patients were stratified according to initial 25(OH)D and evaluated using the same multivariable mixed-effect logistic regression model, the 30-day mortality rate significantly decreased for each 10 ng/mL increase in 25(OH)D (Table 2). For patients with an initial 25(OH)D concentration of 0–11.99 ng/mL, there was a relative decrease in the mortality rate of 30% [OR 0.70, 95% CI 0.52–0.93; $P = 0.015$]; for 12–19.99 ng/mL, of 27%; and for 20–29.99 ng/mL, of 23% (Table 2). The <12 ng/mL cut point was chosen based on literature precedent [17,26–29]. In patients with initial 25(OH)D ≥ 30 ng/mL, multivariable mixed-effect logistic regression analysis showed that the 30-day mortality rate was not significantly altered for each 10 ng/mL increase in 25(OH)D during the year prior to hospitalization (Table 2).

3.2. Secondary outcomes

We evaluated cohort patients with initial 25(OH)D < 20 ng/mL [22] to determine if outcomes varied with increasing time from hospital admission. When patients were evaluated using a multivariable mixed-effect logistic regression model, the in-hospital mortality rate significantly decreased for each 10 ng/mL increase in pre-hospital 25(OH)D [OR 0.74, 95% CI 0.62–0.88; $P = 0.001$] (Table 3). When survivors of hospitalization were evaluated using the multivariable mixed-effect logistic regression model, the 30- and 90-day post-discharge mortality rate were both non-significantly decreased but the effect size diminished with further time from discharge date (Table 3).

Patients with initial 25(OH)D < 20 ng/mL who were subsequently prescribed ergocalciferol or cholecalciferol had a higher likelihood of having an increase of 25(OH)D concentrations ≥ 10 ng/mL in the year leading to hospitalization relative to those without prescriptions (65% vs. 35% respectively; $P < 0.001$). Patients with initial 25(OH)D < 20 ng/mL who were subsequently prescribed ergocalciferol or cholecalciferol had a non-significantly lower odds of 30-day post hospitalization mortality (OR 0.57; 95% CI 0.32–1.00; $P = 0.054$) following adjustment for age, race, gender, Deyo-Charlson Index, and patient type relative to patients who did not have a record of prescribed ergocalciferol or cholecalciferol.

In patients with initial 25(OH)D < 20 ng/mL, a change in pre-hospital 25(OH)D concentration ≥ 10 ng/mL in the year leading to hospitalization was a strong predictor of 30-day mortality (Table 4). The crude odds of 30-day mortality in patients with a change in 25(OH)D concentration ≥ 10 ng/mL were 50% less than that of patients with a change of <10 ng/mL [OR 0.50 (95%CI 0.29–0.85); P = 0.011]. A change in 25(OH)D concentration ≥ 10 ng/mL remained a significant predictor of the odds of 30-day mortality after adjustment for age, race, gender, Deyo-Charlson Index and patient type. The adjusted odds of 30-day mortality in the group of patients with a change in 25(OH)D ≥ 10 ng/mL was 48% less that of patients with a change of <10 ng/mL [OR 0.52 (95%CI 0.30–0.93); $P = 0.026$] (Table 4). Patients with initial 25(OH)D ≥ 20 ng/mL did not have a significant change in the odds of 30-day mortality with a change in 25(OH)D concentration > 10 ng/mL (data not shown). Though limited by statistical power, the results did not materially differ by hospital site (data not shown). The Kaplan-Meier plot (Fig. 1) demonstrating survival grouped according to change in 25(OH)D in the cohort shows a significant difference between the two curves ($P < 0.001$). LOWESS plot (Fig. 2) shows a near linear association between the change in 25(OH)D and the 30-day all-cause mortality rate.

In patients with initial 25(OH)D < 20 ng/mL, we next assessed the odds of death in a smaller cohort of propensity score matched patients ($n = 1278$) (Supplemental Table 1). In propensity score matched patients, the unadjusted 30-day mortality rates were 2.03% (95% CI, 0.9–3.1; 13 deaths) in patients with a change in 25(OH)D ≥ 10 ng/mL versus 4.1% (95% CI, 2.5–5.6; 26 deaths) in patients with a change in 25(OH)D < 10 ng/mL. The crude odds of 30-day mortality in the group of propensity score matched patients with a change in 25(OH)D ≥ 10 ng/mL was 51% less that of patients with a change of <10 ng/mL [OR 0.49 (95%CI 0.25–0.96); $P = 0.038$]. Following additional adjustment, the odds of 30-day mortality in the propensity score matched patients with a change in 25(OH)D ≥ 10 ng/mL was 52% less that of patients with a change of <10 ng/mL[OR 0.48 (95%CI 0.24–0.97); $P = 0.040$] (Table 4).

In patients with initial 25(OH)D < 20 ng/mL, increasing 25(OH)D prior to hospitalization was associated with decreased LOS. In unadjusted analysis, patients with an increase of 25(OH)D prior to hospitalization by ≥ 10 ng/mL stayed in the hospital 1.6 days fewer than patients with 25 (OH)D < 10 ng/mL increase [actual LOS 6.4 (SD 8.1) days vs. 8.0 (SD 12.5) days; $P < 0.001$]. The mean difference between actual LOS and expected LOS in patients with a change in pre-hospital 25(OH)D ≥ 10 ng/mL was 1.5 (SD 6.2) days compared to 2.8 (SD 10.2) in patients with a change in pre-hospital 25(OH)D < 10 ng/mL (P < 0.001). Further, in a mixed-effect linear regression model adjusted for age, gender, race, Deyo-Charlson Index and chronic kidney disease, the actual LOS decreased by 0.4 days (95%CI 0.29–0.49) compared with the expected LOS for the DRG for each 10 ng/mL increase in pre-hospitalization 25(OH)D ($P < 0.001$).

4. Discussion

In our cohort of adult inpatients, we sought to characterize the relationship between an increase in 25(OH)D concentrations during the year leading to hospitalization and the odds of mortality following hospital admission. Our data suggests that there is significant decrease in the risk of 30-day mortality after hospital admission in patients with serum 25(OH)D < 20 ng/mL whose 25(OH)D serum level increased during the year prior to hospitalization. For those with initial 25(OH)D concentrations ≥ 30 ng/mL, further increases in 25(OH)D do not appear to improve mortality.

Table 2
Logistic mixed-effects model estimating 30-day all-cause mortality associated with a 10 ng/mL increase in 25(OH)D stratified by initial 25(OH)D.

	Mortality odds ratio (95% CI)[a]	P-value	Mean (SD) change in 25(OH)D[b]
Initial 25(OH)D			
0–192 ng/mL (n = 4344)	0.92 (0.85–0.99)	0.028	7.5 (16.9)
0–11.99 ng/mL (n = 822)	0.70 (0.52–0.93)	0.015	15.8 (16.8)
12–19.99 ng/mL (n = 1181)	0.73 (0.56–0.95)	0.021	12.6 (15.8)
20–29.99 ng/mL (n = 1093)	0.77 (0.61–0.98)	0.034	7.4 (14.6)
≥30 ng/mL (n = 1248)	1.14 (0.98–1.31)	0.073	2.7 (14.7)

[a] All models were mixed-effect logistic regression models adjusted for age at hospitalization, gender, race and type (medical/surgical). Deyo-Charlson index, hematocrit, and creatinine as well as the random-effects structure.
[b] Change in 25(OH)D is the Mean (SD) absolute difference from initial 25(OH)D to the 25(OH)D drawn closest to hospital admission.

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Table 3
Logistic mixed-effects model estimating mortality associated with a 10 ng/mL increase in 25(OH)D in patients with initial 25(OH)D < 20 ng/mL (n = 1944).

	Mortality odds ratio (95% CI)[a]	P-value
In hospital mortality	0.76 (0.63–0.91)	0.003
30-day mortality following hospital admission	0.74 (0.62–0.88)	0.001
30-day post-discharge mortality[b]	0.82 (0.66–1.01)	0.059
90-day post-discharge mortality[b]	0.90 (0.80–1.01)	0.080

[a] All models were mixed-effect logistic regression models adjusted for age at hospitalization, gender, race and type (medical/surgical). Deyo-Charlson index as well as the random-effects structure. Analysis limited to patients with initial 25(OH)D 0–19.99 ng/mL.
[b] Exclusive of the 104 patients who expired in the hospital.

Table 4
Unadjusted and adjusted associations between an increase in 25(OH)D of ≥10 ng/ml and mortality in patients with initial 25(OH)D < 20 ng/mL (n = 1944).

	Mortality odds ratio (95% CI)[a]	P
30-day mortality		
Crude	0.50 (0.29–0.85)	0.011
Adjusted[b]	0.52 (0.30–0.93)	0.026
PS Matched Cohort[c]	0.49 (0.25–0.96)	0.038
PS Matched Cohort + adjustment[d]	0.48 (0.24–0.97)	0.040
90-day mortality		
Crude	0.51 (0.35–0.75)	0.001
Adjusted[b]	0.54 (0.36–0.80)	0.002
PS Matched Cohort[c]	0.49 (0.30–0.79)	0.004
PS Matched Cohort + Adjustment[d]	0.46 (0.28–0.77)	0.003

Note: PS, Propensity score calculated to estimate the probability for the presence or absence of an increase in 25(OH)D ≥ 10 ng/ml.
[a] Referent in each case is absence of an increase in 25(OH)D ≥ 10 ng/ml.
[b] Model 1: Estimates adjusted for age, gender, race (white, non-white), Deyo-Charlson index, and type (surgical vs. medical).
[c] n = 1,278, with 639 without an increase in 25(OH)D ≥ 10 ng/ml and 639 with an increase in 25(OH)D ≥ 10 ng/ml
[d] PS Matched Cohort additionally adjusted for age, gender, race, Deyo-Charlson index, and type (surgical vs. medical).

We have previously shown that hospitalized patients with low serum 25(OH)D concentrations are at higher risk for mortality, community acquired infection, and healthcare-associated infections [8,18]. Biological evidence shows that in vitmain D deficiency, macrophage function is depressed, specifically with regard to phagocytosis, chemotaxis and proinflammatory cytokine production [30]. The findings of an inverse relationship between 25(OH)D concentrations and vascular endothelial function, endothelium-dependent dilation, and vascular endothelial inflammation may relate to the heightened mortality risk observed with vitamin D deficiency [31].

The potential study limitations are related to the observational design, such as potential reverse causation, confounding and the absence of a randomly-distributed exposure. As the cohort patients had vitamin D status measured for unknown reasons that may not be present in other patients, ascertainment bias may exist. The study was performed in two Boston teaching hospitals and thus the results may not be applicable to other settings (e.g., rural hospitals). Further, as only a small minority of patients who were hospitalized at BWH and MGH during the study were included in the study cohort thus limiting generalizability of our findings to all hospitalized patients. Residual confounding may be present despite multivariable adjustment, which may account for some of the observed differences in outcomes. While chronic kidney disease progression can impact 25(OH)D levels, we have limited data prior to hospitalization to determine disease progression on the cohort. We are also not able to adjust for some variables that can alter 25(OH)D concentrations, including sun exposure, immobilization, excessive alcohol intake, smoking status or genetic factors [32]. A further potential limitation is that 25(OH)D concentrations were not drawn at the time of hospital admission. We also do not have any information as to why 25(OH)D concentrations were obtained. While the Deyo-Charlson Index may account for chronic conditions, it is not clear if severity of illness may influence 25(OH)D concentrations at hospital admission [33].

The present study has several strengths and is unique in that it incorporates multiple measures of 25(OH)D concentrations to investigate the effect of a change in pre-hospital vitamin D status on 30-day all-cause mortality after hospitalization. This is important as the half life of 25(OH)D is 2–3 weeks and 25(OH)D concentrations change depending on diet, season and sun exposure, and supplementation, and a single level does not capture these effects. Our study is adequately powered to detect a clinically relevant difference in 30-day all-cause mortality if one exists.

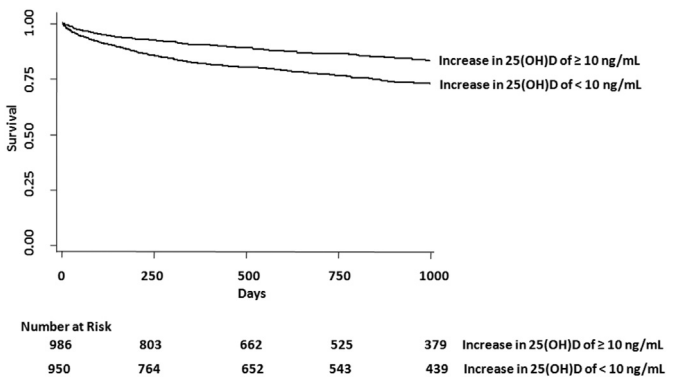

Fig. 1. Time-to-Event curves for mortality in patients with initial 25(OH)D < 20 ng/mL (n = 1944). Unadjusted event rates were calculated with the use of the Kaplan–Meier methods and compared using the log-rank test. The global comparison log rank P-value is < 0.001.

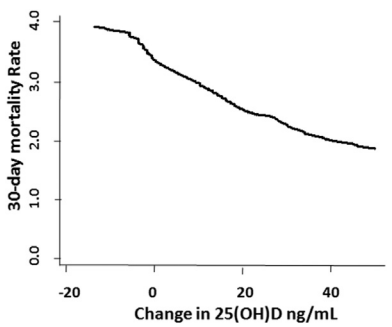

Fig. 2. Change in 25(OH)D concentration versus 30-day all-cause mortality rate. Locally weighted scatter plot smoothing (LOWESS) utilized to represent the near linear association between change in pre-hospital serum 25(OH)D concentration and 30-day all-cause mortality rate in patients with initial 25(OH)D < 20 ng/mL (n = 1944).

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Furthermore, we utilized mixed-effects logistic regression models to investigate differences in 30-day all-cause mortality, since multiple pre-hospital 25(OH)D assessments for each patient are correlated. In addition, mixed-effects models are well suited for longitudinal data because each patient may have an unequal number of observations, and patients with more than two 25(OH)D draws will contribute more accurate information to parameter estimations.

5. Conclusions

In this two-center study of 4344 hospitalized patients, we demonstrate that in those with pre-hospital 25(OH)D concentrations < 20 ng/mL, an improvement in vitamin D status during the year leading up to hospitalization is independently associated with improved all-cause mortality rate and decreased hospital LOS. Further studies are needed to confirm our observations, establish causation, and explore the mechanisms that may explain our findings. While our study is not able to determine causation nor be considered high level evidence in favor of vitamin D supplementation, the combination of the biological evidence, the recent VITdAL-ICU trial [17] and our clinical data presented herein supports the rationale for randomized, controlled trials to study the potential health benefits of vitamin D supplementation in patients before hospitalization.

Disclosure statement

The authors have nothing to disclose.

Conflict of interest

No conflict of interest is present for any of the authors.

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KA, AAL, SAQ, CAC, EG, and KBC designed research; TM, KBC conducted research; KBC and FKG provided essential materials; KBC performed statistical analysis; KA, AAL, TM, SAQ, FKG, TRP, CAC, EG, and KBC wrote the paper; and KBC had primary responsibility for final content. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2015.03.020

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