Original Research

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Association between Vitamin D Deficiency and Prognosis after Hip Fracture Surgery in Older Patients in a Dedicated Orthogeriatric Care Pathway

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Abstract

OBJECTIVES: Vitamin D deficiency is common in patients undergoing hip fracture surgery (HFS) and has been found to be associated with poor post-operative outcome in other settings. This study aimed to analyze the association between vitamin D status and prognosis after HFS.
DESIGN: Observational, prospective, single-center study.
SETTING AND PARTICIPANTS: All patients admitted in a peri-operative geriatric unit between 2009 and 2020 for HFS were included.
MEASUREMENTS: A moderate vitamin D deficiency was defined by a vitamin D level between 25 and 75 nmol/l and a severe deficiency by a vitamin D level <25 nmol/l. Primary endpoint was mortality 6 months after surgery. Secondary endpoints were bacterial infections and delirium during hospitalization. Odds ratio (OR) and 95% confidence interval (95%CI) were computed using logistic regression models with adjustment for confounders.
RESULTS: 1197 patients were included (median age 87 years, IQR [82-91]). Median vitamin D level was 55 nmol/l (IQR [30-75 nmol/l]). Moderate and severe vitamin D deficiencies were reported in 53% and 21% of patients, respectively. There was no significant association between moderate or severe vitamin D deficiencies and 6-month mortality (OR 0.91, 95%CI [0.59-1.39], and OR 1.31, 95%CI [0.77-2.22], respectively), bacterial infection (OR 0.89, 95%CI [0.60-1.31] and OR 1.55, 95%CI [0.99-2.41], respectively), nor delirium (OR 1.03, 95%CI [0.75-1.40], and OR 1.05, 95%CI [0.70-1.57], respectively).
CONCLUSION: Vitamin D deficiency was not associated with mortality, bacterial infection or delirium after HFS. Our results suggest that comorbidities, functional status and post-operative complications are the main determinants of post-operative outcome after HFS.

Key words: Vitamin D, hip fracture, mortality, bacterial infection, delirium.

Introduction

Hip fracture (HF) is a major public health concern affecting more than 1.6 million people each year worldwide, predominantly affecting the older population (1). It is one of the most severe osteoporotic fracture, and is responsible for high morbidity (2) and mortality (3). Vitamin D deficiency is a frequent and easily treatable condition that could affect 1 billion people around the world (4). Up to 86% of older patients undergoing planned or traumatic orthopedic surgery present with vitamin D deficiency (i.e. <75 nmol/l), which mainly affects older patients with multiple comorbidities, including osteoporosis (5). Vitamin D receptor being expressed in most body tissues, the association between vitamin D and outcome in various diseases has been widely studied (4, 6–8).

Vitamin D deficiency is thus associated with all-cause mortality in the general population (9), as well as in patients with various chronic diseases, such as hypertension, diabetes, cardiovascular diseases, cognitive impairment (10) and osteomalacia (11). In patients with HF, the impact of vitamin D on overall mortality is still under debate. One study found a correlation between hyperparathyroidism associated with vitamin D deficiency and 1-year mortality (12). Another study found higher 1-year mortality in patients with severe (i.e. <25 nmol/l) or moderate (25 to 50 nmol/l) vitamin D deficiencies (13). Other studies could not find any association between low vitamin D levels and short- (14) or long-term (15) mortality. However, most studies did not perform adjustment on a high number of comorbidities (13, 14, 16), nutritional parameters (13, 14, 16), frailty (13–16), functional status (13, 14, 16), or other post-operative complications (13–16).

It is assumed that vitamin D could play a role in immune response following viral and bacterial infections, as some observational studies found an association between vitamin D deficiency and occurrence of infectious diseases (17, 18). Patients with vitamin D deficiency experience more frequently respiratory infections (19), and vitamin D supplementation could reduce the risk of these infections (20). A study on patients experiencing non-cardiac surgery found an increased risk of post-operative bacterial infection among patients with vitamin D deficiency, but this association has been scarcely studied after HF surgery (21).

Evidence for a neurosteroïd action of vitamin D on the central nervous system has recently been reported (22).

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Vitamin D deficiency was shown to increase the risk of poor cognitive performance and accelerate cognitive decline (23, 24). A study on 351,320 adults in the United Kingdom found an increased incidence of delirium among patients with vitamin D deficiency (25). Low vitamin D levels were common in patients experiencing delirium (26). Quraishi et al. found an association between low vitamin D levels and occurrence of delirium in hospitalized patients (27). To the best of our knowledge, only one other study evaluated the relationship between delirium and vitamin D deficiency in older patients after HF surgery (28). This study found an association between vitamin D deficiency and post-operative delirium in patients with HF, but the models were adjusted on a few number of cofounders (28).

The aim of our study was to assess the association between vitamin D deficiency and 6-month mortality in older patients after HF surgery in a dedicated orthogeriatric care pathway, taking into account key prognostic factors. We also aimed to study the associations between vitamin D deficiency and other outcomes seldom studied in this context, such as bacterial infection and delirium. We hypothesized that vitamin D deficiency would not be associated with poor outcomes when comorbidities, functional status, frailty, nutritional parameters and post-operative complications are taken into account.

Material and Methods

Population

This observational study was conducted in a 10-bed perioperative geriatric unit (Unit of Peri-Operative Geriatric Care, UPOG) of a teaching hospital in France. The database was created in 2009 in Assistance Publique des Hôpitaux de Paris, and declared with the French national data protection authority (CNIL, Paris, France, n°20190426181554). All patients were informed of their inclusion in the database and had the right to refuse. All consecutive patients aged 70 years and over admitted in our UPOG from July 2009 to August 2020 after HF surgery were screened for eligibility. Individuals with multiple, metastatic or peri-prosthetic fractures were excluded. Detailed methodology has previously been described (29). Some participants have been included in previous studies (supplementary material S1) (29, 30). The present analysis was performed without any funding nor grant.

Baseline characteristics were prospectively collected by interviewing patients, family members, physicians and pharmacists on age, gender, home or nursing home living situation, walking ability, medical history, treatment, and type of fracture (defined radiologically by an orthopedic surgeon). Comorbidity, frailty, and functional scores before HF were determined at hospital admission. Functional status was assessed using Katz's Index of Activities of Daily Living (ADL) and the 4-item Instrumental Activities of Daily Living (IADL) scale.(31, 32). Frailty was assessed using Rockwood's Clinical Frailty Scale (33). Comorbidity burden was measured using the Charlson Comorbidity Index (34).

Surgical and perioperative data was prospectively collected on type of fracture and surgery, time from fracture to surgery, duration of surgery, type of anesthesia (general vs. spinal), and number of packed red blood cells administered. Post-operative data included time to ambulation, occurrence of post-operative delirium or bacterial infection, percentage of patients discharged to home, length of stay in acute care and rehabilitation departments.

Serum 25-hydroxyvitamin D (25-OH vitamin D) was routinely measured at admission in UPOG using an immunoenzymatic automatic test. Its dosage is integrated in the peri-operative care plan, to guide vitamin D supplementation according to a local protocol, which has not changed since the creation of the database. A moderate vitamin D deficiency was defined by a vitamin D level between 25 and 75 nmol/l (or 10 and 30 ng/ml) and a severe deficiency by a vitamin D level lower than 25 nmol/l, according to the most frequently used thresholds (6). Since previous studies found that patients with the most severe vitamin D deficiencies had the greatest risks of poor post-operative outcome, we chose to separate patients with severe vitamin D deficiency (i.e. less than 25 nmol/l) from patients with moderate vitamin D deficiency (i.e. less than 75 nmol/l) (13, 16).

Primary and secondary endpoints

Primary endpoint was 6-month mortality. Secondary endpoints were occurrence of post-operative delirium and bacterial infection during UPOG stay. Post-operative delirium was defined according to Confusion Assessment Method (CAM)(35) which was performed upon arrival at UPOG then daily during UPOG stay by one of the two orthogeriatric experts (JCB, JB). Diagnosis of bacterial infection was performed by at least one orthogeriatric expert during the patient's stay in our unit and based on the presence of fever or systemic inflammatory response and: (i) for pneumonia, at least one respiratory symptom (cough, dyspnea, sputum, or asymmetrical crackles at lung auscultation) and a new radiographic pulmonary infiltrate (chest X-ray or computed tomography scan); (ii) for urinary tract infection, significant bacteriuria (>104 colony forming unit [CFU]/mL or >103 CFU/mL for non-Coli bacteria in women) and urinary white cells count (>104/mL) associated with urinary symptoms (dysuria, hematuria, back pain) or no other obvious site of infection; (iii) for biliary infection, radiological diagnosis of cholecystitis or cholangitis (ultrasound or computed tomography scan); (iv) for erysipelas, description of an acute inflammation of a skin area; (v) for diverticulitis, radiological diagnosis using computed tomography scan; (vi) for surgical site infection, microbiological evidence of surgical site infection from cultures obtained aseptically. A few cases did not fulfill all the mentioned criteria but were considered as bacterial infection by the experts.

Outcome was prospectively collected during hospitalization, and patients were followed-up with a systematic consultation 1 and 6 months after surgery. Missing patients were contacted and interviewed by phone, or by calling health care providers or acquaintances.

Statistical analysis

Data are expressed as median [25-75 interquartile] for quantitative variables or mean ± SD in case of normal distribution (determined by a Shapiro-Wilk test), and number (percentages) for categorical variables. Characteristics of patients with normal vitamin D levels (i.e. > 75 nmol/l), moderate vitamin D deficiency and severe vitamin D deficiency were compared using analysis of variance or Kruskal-Wallis test as appropriate for continuous variables and chi-square tests for categorical variables.

Cumulative incidence curves were then computed and compared according to vitamin D levels for death 6 months following surgery. Endpoints were then analyzed using logistic regression models. Logistic regression models were adjusted for variables known or suspected to be confounders for the association between vitamin D level and each endpoint (supplementary material S2) (30).

Linearity of association between endpoints and continuous or ordinal variables were evaluated (including vitamin D levels). If the linearity hypothesis was rejected, the population was categorized into two groups according to the cut-off of the variable maximizing the sensitivity and specificity for the association with the considered endpoint. The variables retained for multivariate analysis were vitamin D deficiency and variables associated with the endpoint with a p value <0.10 in the univariate analysis. Bootstrapping was used to compute 95%CI, as appropriate (36). Models finally retained were those that minimized the Akaike Information Criterion. Collinearity was assessed by computing the Variance Inflation Factor (VIF), but VIF were low (<2) for each variable retained in the final models. Discrimination of retained multivariable models was assessed using C statistics. Calibration of retained multivariable models were assessed graphically by using calibration plots. Sensitivity analyses were performed for each endpoint by using vitamin D levels maximizing the sensitivity and specificity for the association with the studied endpoint. Sensitivity analysis was performed by studying the association between vitamin D deficiency and 1-month mortality, which we thought would be less influenced by vitamin D supplementation than after 6 months, as vitamin D level was available only during hospitalization and not during follow-up.

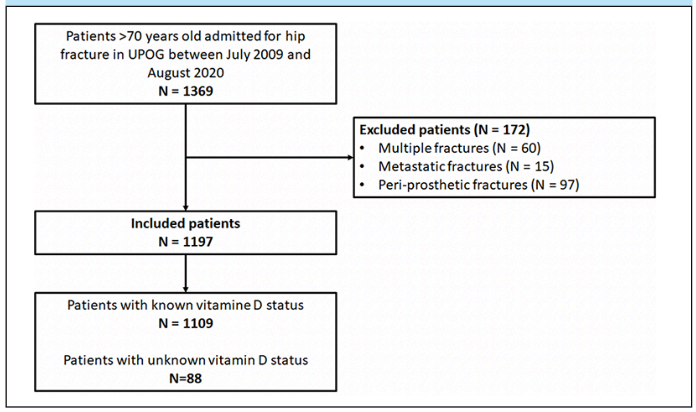
Missing values were taken into account by computing multiple imputations using multiple chained equations. For each missing value, 20 imputations were computed, leading to 20 different databases. The results of the 20 databases were pooled according to Rubin's rules (37). We chose to keep in the main analysis patients with missing values for vitamin D levels, as appropriate (38, 39). However, another sensitivity analysis was performed in patients without missing values for vitamin D. A p value <0.05 was considered statistically significant (two-tailed test). Statistical analyses were performed using R software (R Foundation, Vienna, Austria, version 4.0.2).

Results

Population

During the study period, 1369 patients were admitted in UPOG after HF surgery. Among them, 172 (13 %) were excluded for multiple, metastatic or peri-prosthetic fractures (figure 1), thus 1197 patients were finally retained for analysis. Baseline characteristics are presented in table 1. Median vitamin D level was 55 nmol/l [30 – 75 nmol/l]. Moderate and severe vitamin D deficiencies were reported in 629 (53%) and 249 (21%) patients, respectively. Patients with moderate and severe vitamin D deficiencies were more likely to be male and younger, had a lower delay before surgery and were less frequently treated by selective serotonin reuptake inhibitors than patients without vitamin D deficiency (table 1). Median length of stay in UPOG was 9 days [7 – 13]. Discharge to home occurred in 196 (16%) patients, and 946 patients (79%) were transferred to a rehabilitation center. Death occurred in 55 (5%) patients during UPOG stay.

Figure 1. Study flowchart



UPOG: Unit of Peri-Operative Geriatric Care

Primary outcome

Fifty-one patients (16%) without vitamin D deficiency died within six months following surgery, compared to 94 patients (15%) in the moderate vitamin D deficiency group and 47 (19%) in the severe deficiency group (p=0.30 by comparing cumulative incidence curves; figure 2).

After adjustment for confounders, moderate or severe vitamin D deficiencies were not significantly associated with 6-month mortality (table 2, supplementary table S1). Discrimination and calibration of the final model were good (supplementary table S1 and figure S1). Our results were not modified when using the cut-off maximizing sensitivity and specificity (i.e. 55 nmol/L, table 2).

Secondary outcomes

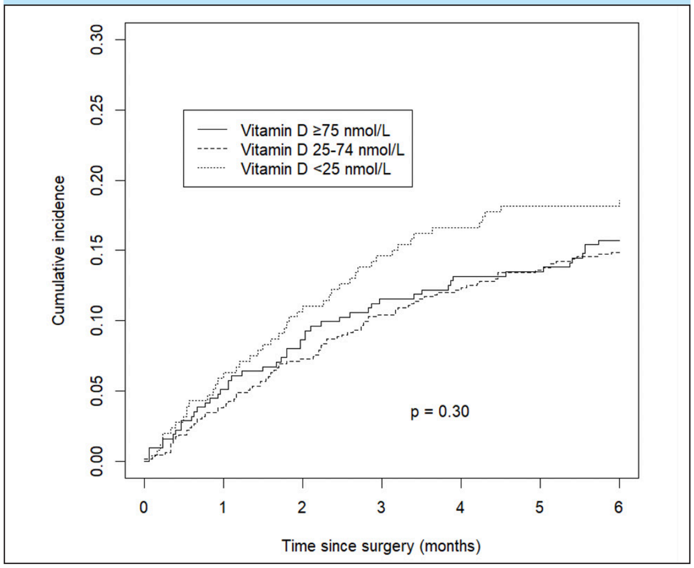
Bacterial infections occurred in 51 patients (16%) with no vitamin D deficiency, 88 (14%) patients with moderate

Table 1. Demographic data and baseline characteristics of older patients included in the cohort and stratified by vitamin D status

Characteristics*	All participants n = 1197	Vitamin D < 25 nmol/l n = 249 (20.8%)	Vitamin D 25-74 nmol/l n = 629 (52.5%)	Vitamin D ≥ 75 nmol/l n = 319 (26.6%)	P-value	Missing data, n (%)
Age	87 [82-91]	86 [82-90]	87 [82-91]	87 [83-91]	0.048	0 (0)
Male	290 (24)	90 (36)	140 (22)	60 (19)	<0.001	0 (0)
Female	907 (76)	159 (64)	486 (78)	259 (81)	<0.001	0(0)
Vitamin D (nmol/l)	55 [30-75]	15 [10-18]	53 [40-60]	90 [83-100]		
Missing values	88 (7)	19 (8)	47 (7)	22 (7)		
Medical history						
Neurocognitive disorder	494 (41)	100 (40)	262 (42)	132 (41)	0.91	0 (0)
Depression	370 (31)	68 (27)	188 (30)	114 (36)	0.09	0 (0)
Parkinson	70 (6)	15 (6)	40 (6)	15 (5)	0.54	0 (0)
Hypertension	814 (68)	160 (64)	443 (71)	211 (66)	0.15	0 (0)
Diabetes mellitus	169 (14)	44 (18)	90 (14)	36 (11)	0.11	0 (0)
Obesity	73 (6)	19 (8)	43 (7)	11 (3)	0.06	0 (0)
Atrial fibrillation	333 (28)	61 (25)	184 (29)	88 (28)	0.40	0 (0)
Coronary artery disease	220 (18)	45 (18)	121 (19)	54 (17)	0.66	0 (0)
Heart failure	200 (17)	35 (14)	111 (18)	53 (17)	0.47	0 (0)
Stroke	214 (18)	49 (20)	98 (16)	67 (21)	0.09	0 (0)
Venous thromboembolism	86 (7)	16 (6)	41 (7)	29 (9)	0.29	0 (0)
Peripheral artery disease	90 (8)	17 (7)	47 (8)	26 (8)	0.91	0 (0)
COPD	90 (8)	12 (5)	46 (7)	31 (10)	0.13	0 (0)
MDRD (ml.min-1.1.73m-2)	82 [63-105]	80 [64-98]	82 [63-107]	87 [63-103]	0.38	0 (0)
Cancer	265 (22)	54 (22)	139 (22)	73 (23)	0.93	0 (0)
Alcohol consumption	38 (3)	12 (5)	17 (3)	9 (3)	0.23	0 (0.0)
Blindness	74 (6)	18 (7)	33 (5)	24 (7)	0.38	0 (0.0)
Serum albumin (g/l)	29 [26-31]	29 [25-32]	29 [26-31]	29 [27-31]	0.35	
Missing values	45 (4)	10 (4)	23 (4)	12 (3.7)		
Charlson comorbidity index	7 [4-8]	7 [4-8]	7 [5-8]	7 [5-8]	0.60	0 (0.0)
Psychiatric treatment						
Selective serotonin reuptake inhibitor	299 (25)	41 (17)	160 (25)	98 (31)	0.001	
Missing values	1 (0)	0 (0)	1 (0)	0 (0)		
Benzodiazepine	276 (23)	54 (22)	140 (22)	82 (26)	0.44	
Missing values	1 (0)	0 (0)	1 (0)	0 (0)		
Hypnotic	186 (16)	37 (15)	109 (17)	40 (13)	0.18	
Missing values	1 (0)	0 (0)	1 (0)	0 (0)		
Neuroleptic	62 (5)	12 (5)	29 (5)	21 (7)	0.54	
Missing values	1 (0)	0 (0)	1 (0)	0 (0)		
Functional status						
ADL (0 to 6)	5.5 [3.5-6]	5.5 [3.5-6]	5.5 [3.5-6]	5.5 [3.5-6]	0.68	0 (0)
IADL (0 to 4)	2.0 [0-4]	2.0 [1-3]	2.0 [0-4]	2.0 [0-4]	0.81	
Missing values	3 (0)	1 (0)	1 (0)	1 (0)		
Nursing home resident	173 (15)	27 (11)	98 (16)	48 (15)	0.17	0 (0)
Rockwood scale	5 [4-6]	5 [4-6]	5 [4-6]	5 [4-6]	0.45	
Missing values	1 (0)	0 (0)	1 (0)	0 (0)		
Surgery						
General anesthesia	1160 (97)	240 (96)	613 (97)	308 (96)	0.66	
Missing values	100 (8)	20 (8)	52 (8)	28 (9)		
Femoral neck fracture	563 (47)	130 (52)	303 (48)	130 (41)	0.02	0 (0)
Pertrochanteric fracture	634 (53)	119 (48)	323 (52)	189 (59)	0.02	0 (0)
Hospital-surgery delay (hours)	26 [18-46]	24 [15-43]	27 [19-48]	28 [19-46]	0.02	
Missing values	9 (1)	2 (1)	5 (1)	2 (1)		

*Data are expressed as median (1st–3rd quartiles) for quantitative variables, and sample size (percentages) for categorical variables; missing values are expressed as sample size (percentages) and only specified for variables with one or more missing values; MDRD: Modification of Diet in Renal Disease Study equation, COPD: Chronic Obstructive Pulmonary Disease, ADL: Activities of Daily Living, IADL: Instrumental Activities of Daily Living vitamin D deficiency and 54 (22%) patients with severe vitamin D deficiency (p=0.02). Bacterial infections included 107 pneumonias, 51 urinary tract infections, 9 biliary infections, 4 erysipelas, 3 surgical site infections, 3 diverticulitis, and 19 infections of other locations (n=196; some infections concomitantly occurred in the same patients). In two patients, a respiratory virus was identified with a concomitant bacterial infection. After adjustment, neither moderate nor severe vitamin D deficiencies were significantly associated with post-operative bacterial infection, comparatively with no deficiency (table 2, supplementary table S2 and figure S2).

Figure 2. Mortality according to vitamin D level after hip fracture surgery – Cumulative incidence curves



Delirium occurred in 137 (43%), 270 (43%) and 105 (42%) patients without vitamin D deficiency, with moderate and severe vitamin D deficiency, respectively (p=0.95). After adjustment for confounders, moderate or severe vitamin D deficiencies were not significantly associated with post-operative delirium, in comparison with no deficiency (table 2, supplementary table S3 and figure S3).

Results were not modified when using cut-offs maximizing sensitivity and specificity in the association between vitamin D and secondary endpoints.

Sensitivity analyses

During the first month of follow-up, 76 (6%) patients died: 20 (6%) with no vitamin D deficiency, 34 (5%) with moderate vitamin D deficiency and 22 (9%) with severe vitamin D deficiency (p=0.18). Moderate and severe vitamin D deficiencies were not associated with 1-month mortality after adjustment for confounders, with an OR = 0.88 (95%CI [0.46-1.70]) for moderate vitamin D deficiency and OR = 1.59 (95%CI [0.75-3.39]) for severe vitamin D deficiency, comparatively with no vitamin D deficiency (supplementary table S4).

Analysis of patients without missing values for vitamin D did not change our results for the study of primary and secondary outcomes (table 3).

Discussion

Among older patients presenting with HF in a dedicated orthogeriatric care pathway, vitamin D deficiency was frequent (73%), yet neither moderate nor severe vitamin D deficiencies were significantly associated with 6-month mortality. Patients with moderate or severe vitamin D deficiencies were not more likely to experience post-operative delirium or bacterial infection. To the best of our knowledge, this study is the largest assessing the prognostic value of vitamin D after hip fracture surgery in older patients, and the first specifically taking place in a dedicated orthogeriatric care pathway.

Vitamin D deficiency rate was similar in our study as what was previously described in literature (15, 40). We found that vitamin D deficiency was more frequent amongst male patients, which was not reported in bigger epidemiologic studies (6) nor in observational studies on hip fracture (41). We did not find any other study that could explain why vitamin D deficiency rate was lower among patients taking selective serotonin reuptake inhibitors. These discordant results could be due to other unmeasured confounding factors that are prevalent in our population, such as other comorbidities or baseline functional status.

Previous studies found opposite results about the association between vitamin D deficiency and mortality after HF surgery (12–16). We previously showed that many factors are associated with 6-month mortality after HF surgery. Among them, baseline characteristics and post-operative complications accounted for 62% and 13% of attributable mortality (30). In a fully-adjusted model, vitamin D was not associated with mortality after HF surgery. Our results suggest that comorbidities, functional status and post-operative complications overweight the burden of severe vitamin D deficiency on mortality in this context. The lack of benefit of vitamin D supplementation in randomized clinical trials (42) suggests that the poorer prognosis associated with vitamin D deficiency found in some previous observational studies may in fact be related to confounding factors such as comorbidities, frailty, and nutritional status.

Among infectious diseases, vitamin D deficiency was mainly found to be associated with respiratory infections (19). In our population, pneumonia represented half of bacterial infections occurring during UPOG stay, mainly due to aspiration pneumonia (43). However, our study did not find a significant association between vitamin D deficiency and post-operative bacterial infections during hospitalization. These results are in contrast with another study performed in the context of non-cardiac surgery (21). In this previous study, patients were younger (mean age 65 years) with only 35% of patients undergoing orthopedic surgery, which could probably explain the difference with our results. Moreover, although the incidence of infectious diseases was lower in the previous study, the absolute number of events was higher than in our cohort. Thus, we cannot totally rule out a lack of statistical power in our study.

Post-operative delirium was associated with vitamin D deficiency after HF surgery in a previously published study,

Table 2. Primary and secondary outcomes depending on vitamin D status

Vitamin D level	Incidence of event (%)	Univariate analysis OR (95%CI)[a]	P-value	Multivariate analysis[b] OR (95%CI)[a]	P-value
6-month mortality					
Vitamin D ≥75 nmol/l	51/319 (16.0)	1		1	
Vitamin D 25-74 nmol/l	94/629 (14.9)	0.92 (0.63-1.34)	0.66	0.91 (0.59-1.39)[d]	0.65
Vitamin D <25 nmol/l	47/249 (19.0)	1.23 (0.80-1.91)	0.35	1.31 (0.77-2.22)[d]	0.32
Vitamin D ≥55 nmol/l[c]	98/604 (14.3)	1		1	
Vitamin D <55 nmol/l	95/593 (16.8)	0.99 (0.72 – 1.34)	0.92	1.20 (0.83-1.72)[d]	0.34
Bacterial infection					
Vitamin D ≥75 nmol/l	51/319 (16.0)	1		1	
Vitamin D 25-74 nmol/l	88/629 (14.1)	0.86 (0.59-1.26)	0.44	0.89 (0.60-1.31)[e]	0.55
Vitamin D <25 nmol/l	54/249 (21.5)	1.44 (0.94-2.23)	0.10	1.55 (0.99-2.41)[e]	0.053
Vitamin D ≥55 nmol/l[c]	90/604 (15.0)	1		1	
Vitamin D <55 nmol/l	103/593 (17.3)	1.19 (0.87-1.63)	0.28	1.24 (0.90-1.71)[e]	0.18
Delirium					
Vitamin D ≥75 nmol/l	137/319 (42.8)	1		1	
Vitamin D 25-74 nmol/l	270/629 (43.0)	1.01 (0.72-1.41)	0.96	1.03 (0.75-1.40)[f]	0.87
Vitamin D <25 nmol/l	105/249 (42.3)	0.98 (0.70-1.37)	0.89	1.05 (0.70-1.57)[f]	0.81
Vitamin D ≥55 nmol/l[c]	277/604 (45.8)	1		1	
Vitamin D <55 nmol/l	236/593 (39.8)	0.78 (0.62-0.99)	0.04	0.88 (0.67-1.14)[f]	0.33

a. OR: odds ratio calculated by logistic regression models; 95% confidence interval (95%CI) were computed using bootstrap; b. logistic regression models were adjusted for variables known or suspected to be confounders for the association between vitamin D level and each endpoint; the variables retained for multivariate analysis were vitamin D and variables associated with the endpoint with a p value <0.10 in the univariate analysis; c. cut-off maximizing the sensitivity and specificity in the association between vitamin D and the event; d. adjusted for sex, age, history of atrial fibrillation, heart failure, cancer, serum albumin, Instrumental Activities of Daily Living, Rockwood scale, post-operative heart failure, post-operative bacterial infection, post-operative atrial fibrillation, and post-operative pressure ulcer; e. adjusted for history of pulmonary disease, hospital-surgery delay, and serum albumin level; f. adjusted for age, history of cognitive impairment, history of depression, Instrumental Activities of Daily Living, delay between hospital and surgery, post-operative urinary retention, and post-operative fecal impaction.

which contrasts with our results (28). This difference could be due to the fact that incidence of post-operative delirium was very low in their population (18%) and prevalence of cognitive impairment was not described (28). Older patients experiencing emergency orthopedic surgery often have multiple risk factors for delirium, such as cognitive impairment, depression, pain, anesthesia, analgesics, anemia, fecal impaction or urinary retention (44). In the light of the burden of multiple risk factors of delirium in a geriatric population during the post-operative period, the impact of vitamin D status could be much less significant.

Besides these problems of possible confounders associated with poor post-operative outcome, the discrepancy of these results could also be explained by the perioperative management of HF. An orthogeriatric co-management in dedicated units allows a coordination between emergency room doctors, anesthesiologists, orthopedic surgeons and geriatricians. This co-management integrates all factors encountered from patient's arrival at the emergency room to its discharge from the geriatric unit. This orthogeriatric co-management has previously been showed to be associated with reduced mortality after HF surgery (29, 45). Thus, it is possible that the association between vitamin D and mortality (and other outcomes) could differ in an orthogeriatric care pathway by comparison with other settings, due to the fact that incidence of post-operative outcomes differs.

The present study has several strengths. It describes a large cohort of older patients with HF with a high proportion of vitamin D deficiency. Vitamin D level was available for most participants, and we used multiple imputation for missing data. A large number of variables were available, which allowed us to assess the effect of specific confounders in each association, which is a major difference with what was previously performed in others studies on patients with HF (12–16). We also must acknowledge several limitations. First, this study was observational which precludes it from demonstrating a causality link. Data was not available on vitamin D supplementation and vitamin D levels during follow-up. Our unit systematically prescribed vitamin D supplementation in case of deficiency according to a protocol which has not changed during the study period, which could have weakened the association between vitamin D level and 6-month mortality. However, we also analyzed short-term mortality, which is supposedly less prone to bias in case of vitamin D supplementation, and have found similar results. Finally, the p-value for the association between bacterial infection and severe vitamin D deficiency was close to 0.05 (table 2). As previously mentioned, we cannot totally exclude the hypothesis that our study lacked sufficient power to detect a small association. Interventional studies are therefore needed to assess the benefit of vitamin D supplementation on the risk of post-operative bacterial infection in this population.

Table 3. Primary and secondary outcomes depending on vitamin D status in patients without missing values for vitamin D

Vitamin D level	Multivariate analysis[a] OR (95%CI)[b]	P-value
6-month mortality		
Vitamin D ≥75 nmol/l	1	
Vitamin D 25-74 nmol/l	0.90 (0.57-1.41)[c]	0.63
Vitamin D <25 nmol/l	1.28 (0.73-2.24)[c]	0.38
Bacterial infection		
Vitamin D ≥75 nmol/l	1	
Vitamin D 25-74 nmol/l	0.89 (0.59-1.32)[d]	0.55
Vitamin D <25 nmol/l	1.57 (0.99-2.50)[d]	0.053
Delirium		
Vitamin D ≥75 nmol/l	1	
Vitamin D 25-74 nmol/l	1.01 (0.73-1.39)[e]	0.96
Vitamin D <25 nmol/l	1.02 (0.67-1.55)[e]	0.93

a. logistic regression models were adjusted for variables known or suspected to be confounders for the association between vitamin D level and each endpoint; the variables retained for multivariate analysis were vitamin D and variables associated with the endpoint with a p value <0.10 in the univariate analysis; b. OR: odds ratio calculated by logistic regression models; 95% confidence interval (95%CI) were computed using bootstrap; c. adjusted for sex, age, history of atrial fibrillation, heart failure, cancer, serum albumin, Instrumental Activities of Daily Living, Rockwood scale, post-operative heart failure, post-operative bacterial infection, post-operative atrial fibrillation, and post-operative pressure ulcer; d. adjusted for history of pulmonary disease, hospital-surgery delay, and serum albumin level; e. adjusted for age, history of cognitive impairment, history of depression, Instrumental Activities of Daily Living, delay between hospital and surgery, post-operative urinary retention, and post-operative fecal impaction.

Conclusions and implications

In this study on older patients with HF surgery in an orthogeriatric setting, and after adjusting for confounding factors, 25-hydroxyvitamin D deficiency was not associated with all-cause 6-month mortality, bacterial infection, or delirium during the stay in our unit. Our results could suggest that comorbidities, functional status and post-operative complications are the main determinants of post-operative outcome after HF surgery.

Conflicts of Interest: The authors declare having no potential source of conflict of interest regarding this article.

Ethical standards: All the experiments in this study comply with the current laws of the country in which they were performed

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