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Original article

The relevance of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentration for postoperative infections and postoperative organ dysfunctions in cardiac surgery patients: The eVIDenCe study

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SUMMARY

Background & aims: Recent studies indicate that vitamin D deficiency is associated with increased morbidity and mortality in critically ill patients. Knowledge about the functional role and clinical relevance of vitamin D for patients undergoing cardiac surgery is sparse. Therefore, we investigated the clinical significance of vitamin D levels on outcome of cardiac surgery patients.

Methods: 92 patients undergoing elective cardiac surgery with cardiopulmonary arrest were included in this prospective observational pilot study. 25-hydroxyvitamin D (25OHD) and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) levels were measured prior to surgery, immediately postoperatively as well as 6, 12 and 24 h after surgery. We assessed postoperative organ dysfunctions, infections and death until hospital discharge.

Results: The serum concentration of $1,25(OH)_2D$ significantly decreased intraoperatively by 29.3% ($p < 0.001$) and was significantly lower at any postoperative time point compared to baseline values, whereas 25OHD levels did not show significant changes during the observation period. Coronary artery bypass graft (CABG) patients had significant higher baseline $1,25(OH)_2D$ values than patients with valve surgery (39.7 ± 13.9 ng/l vs. 30.1 ± 14.1 ng/l, $p = 0.010$) or CABG + valve surgery (39.7 ± 13.9 ng/l vs. 32.6 ± 11.8 ng/l, $p = 0.044$).

Our data showed a significant odds ratio to develop postoperative organ dysfunction (OR 0.95; $p = 0.009$) and PCT levels ≥5 μg/l (OR 0.94; $p = 0.046$) for every ng/l increment in $1,25(OH)_2D$, when performing multivariable analysis and after adjusting for preoperative illness and demographics. In addition, multivariable-adjusted statistical analyses revealed that patients stayed significantly shorter on ICU (−0.21 h; $p = 0.001$) and in hospital (−2.6 days; $p = 0.009$) for every ng/l increment in $1,25(OH)_2D$.

Conclusion: Our data highlight important evidence about the clinical significance of $1,25(OH)_2D$ levels in cardiac surgery patients. Higher levels were associated with significantly less postoperative organ dysfunctions, elevated PCT levels, death and prolonged hospital stay. $1,25(OH)_2D$ levels decreased significantly intra- and postoperatively, while serum levels of 25OHD did not.

Trial registration: clinicaltrials.gov (NCT 02488876), registered May 1, 2015.

Abbreviations: 25OHD, 25-hydroxyvitamin D; 1,25(OH)2D, 1,25-dihydroxyvitamin D; AKI, acute kidney injury; CABG, Coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; GFR, glomerular filtration rate; ICU, intensive care unit; LOS, length of hospital stay; LVAD, left ventricular assist device; OR, odds ratio; PCT, Procalcitonin; PODs, postoperative organ dysfunctions; RAS, renin-angiotensin system.

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1. Background

During the past decades, an impressive body of evidence indicates a critical role of vitamin D levels among critically ill patients [1–4]. Despite the well-known mechanisms of vitamin D, including calcium absorption and bone health metabolism, recent data shows that vitamin D deficiency is associated with a higher incidence of postoperative inflammatory processes [5] as well as adverse clinical outcome in cardiac surgery patients [5–12]. The underlying pathways are not fully understood, however the active vitamin D $1,25(OH)_2D$ demonstrates immune modulating properties in macrophages, leading to an upregulation of vitamin D receptors and 1α-hydroxylase gene expression when exposed to lipopolysaccharides or bacteria [1]. An upregulated activation of $1,25(OH)_2D$ results in cathelicidin synthesis, which in turn is capable of eradicating infectious cells. In addition, a recently published trial [13] described a correlation between $1,25(OH)_2D$ deficiency and a lack of gluthatione, which may result in higher levels of oxidative stress and inflammation.

Cardiac surgery patients are at increased risk to nosocomial infections [14] and surgery related inflammation [15], both resulting in prolonged hospital stay (LOS) and increased mortality [16]; therefore this vitamin may be an important factor for the body's immune defense mechanisms. While 25OHD levels <20 ng/ml have well been demonstrated to be highly prevalent in cardiac surgery patients prior to surgery [17] and 25OHD levels between 20 and 40 ng/ml are associated with the lowest risk of major adverse cardiac and cerebrovascular events (MACCE) [12], knowledge about vitamin Ds perioperative and especially postoperative course, comparison of vitamin D subtypes and data about optimal vitamin D cut-off levels remain sparse [7,18,19] The present study aimed to investigate the pre- and postoperative time course of biological inactive as well as active vitamin D levels and its clinical significance with special focus on the development of organ dysfunctions in cardiac surgery patients.

2. Methods and materials

2.1. Study design and patients

Following approval by the institutional review board (Ethics committee, Medical Faculty, RWTH Aachen University: EK 151/09) and registration at clinicaltrials.gov (NCT 02488876; registered May/1, 2015), patients were enrolled in this observational study. Patients scheduled to undergo elective cardiac surgical procedures between 09/2015 and 04/2016 with the use of cardioplegic-induced cardiac arrest and cardiopulmonary-bypass and willing to sign written informed consent were included. Exclusion criteria were age under 18 years, lack of informed consent, emergency surgery, or pregnancy. Trial content was performed in accordance with the Declaration of Helsinki.

2.2. Anesthesia and cardiopulmonary bypass (CPB)

Anesthesia and intraoperative treatment during cardiac surgery was standardized according to RWTH clinical standards (Supplemental digital content 1).

2.3. Data collection and laboratory assessment

The serum probes were prospectively collected for the later measurements of 25OHD and $1,25(OH)_2D$ at the institute of clinical chemistry (RWTH Aachen). Serum samples were collected preoperatively, directly after surgery (0) as well as 6, 12 and 24 h after admission at the ICU. All blood samples were collected in Serum-Monovettes (Sarstedt AG & Co, Nümbrecht, Germany) and subsequently centrifuged at 3000 rpm for 10 min. The supernatants were filled in Eppendorf tubes (Eppendorf AG, Hamburg, Germany) for storage at −80 °C until further analysis of 25OHD and $1,25(OH)_2D$. Serum samples were finally analyzed by the central laboratory of the University Hospital RWTH Aachen, measured by chemiluminescence-immunoassay method using the Liaison® XL device (DiaSorin, Saluggia, Italy).

2.4. Outcomes and blinding

According to the institute of medicine (IOM) guidelines, 25OHD levels of 20 ng/ml cover the needs of the population and deficiency symptoms may appear at levels less than 30 nmol/l (12 ng/ml) [19]. Since no standardized classification exists to define vitamin D deficiency with respect to clinical outcome, we showed the distribution of 25OHD levels in our cohort. For $1,25(OH)_2D$ deficiency, the cut off is < 20 ng/l.

Postoperative organ dysfunctions, including acute respiratory distress syndrome, acute kidney injury, cardiogenic shock, liver failure, neurologic dysfunction and nosocomial infections, were defined in accordance with the Society of Critical Care Medicine criteria during ICU stay version 3 (Supplemental digital content 2). Data about length of stay in hospital and on ICU and mortality have also been collected. Specific surgery related subgroup analyses were defined before statistical analysis to emphasize the different underlying pathophysiology. While one study physician collected patient data and brought the serum samples to the central laboratory of the University Hospital RWTH Aachen, a second study physician not involved in data collection carried out the statistical analysis.

2.5. Statistical analysis

Categorical variables were summarized by absolute and relative frequencies, continuous variables by mean and standard deviation. Differences in postoperative vitamin D levels compared to baseline levels were analyzed using the one sample t-test. Group differences for baseline characteristics, type of surgery and postoperative outcome were analyzed by unpaired t-test for continuous parameters and by Fishers Exact Test for categorical data. Statistical analyses with regard to descriptive statistics were performed using IBM SPSS Version 20 (IBM Corporation, Armonk, NY, USA).

We identified possible important covariates using univariate Firth's bias-reduced logistic regression for each binary outcome separately: organ dysfunction, infection and death. Covariates with a p-value of less than 0.2 were then included in multivariable Firth's bias-reduced logistic regression models. Significant interaction between covariates and $1.25(OH)_2D$ were considered. We chose three separate multivariable models due to the large number of possible important covariates. The continuous outcomes hospital stay and ICU stay were analyzed by ANCOVA. Due to the exploratory nature of the study, we assessed a 5% significance level for each model. These statistical analyses were performed using SAS software, version 9.4 Figures were composed using GraphPad PRISM® Version 6 (GraphPad Software Inc., La Jolla, CA, USA).

3. Results

3.1. Patient cohort and baseline characteristics

Ninety-two patients were enrolled in this prospective trial (Fig. 1). Baseline and operative characteristics are shown in

Tables 1 and 2, demonstrating that the included patients reflect a representative cohort of cardiac surgical patients with typical co-morbidities and co-medications. In addition, we investigated preoperative vitamin D levels with regard to the season of the year. 25OHD levels were significantly lower in the spring (9.19 ng/ml, n = 21) compared to 25OHD levels in autumn (15.4 ng/ml, n = 38, p = 0.001) and winter (13.13 ng/ml, n = 33, p = 0.041). With respect to 1,25(OH)2D no significant differences have been observed.

3.2. Serum levels of vitamin D in cardiac surgery patients

With regard to 25OHD, our results demonstrate that 97.8% of the cardiac surgery patients had 25OHD levels <30 ng/ml, 83% showed levels <20 ng/ml and even 60% had levels <12 ng/ml preoperative as shown in Fig. 2A. 25OHD serum levels started at 13.2 ± 7.2 ng/ml in average, showed a mild, but non-significant decrease to 12.3 ± 5.9 ng/ml postoperatively and did not further change significantly at 24 h after surgery (Fig. 2B).

With regard to serum levels of $1,25(OH)_2D$ only 19.6% of patients showed a deficiency (<20 ng/L) before surgery (Fig. 2C,D). Mean circulating serum levels of $1,25(OH)_2D$ were 33.6 ± 14.2 ng/l before surgery and demonstrated a continuous decrease at any time point after surgery compared to baseline values. Lowest $1,25(OH)_2D$ levels were observed 24 h postoperatively (18.1 ± 8 ng/l, p = 0.000), resulting in 63.5% with $1,25(OH)_2D$ deficiency (Fig. 2C,D). When further analyzed, it turned out that $1,25(OH)_2D$ serum levels of patients without preoperative deficit (≥20 ng/l) decreased by 47.5% in the 24 h after surgery (38.8 ± 10.4 ng/l to 20.4 ± 7.2 ng/l; p < 0.0011) but in average still remained above the lower reference limit of 20 ng/l. Among patients with preoperative low $1,25(OH)_2D$ concentration (<20 ng/l) serum levels further decreased until 24 h after surgery by 32.1% (12.3 ± 4.8 ng/l to 8.4 ± 2 ng/l, p < 0.001) resulting in a severe deficiency.

In order to further identify patients at high risk to develop vitamin D deficiency, we investigated to what extent the type of surgery had an effect. Data shows that $1,25(OH)_2D$ serum values were significantly lower in patients undergoing CABG combined with valve surgery (32.7 ± 11.8 ng/l, p = 0.044) or valve surgery (30.1 ± 14.1 ng/l, p = 0.010) compared to isolated CABG surgery (39.7 ± 13.9 ng/l, Fig. 3A). With regard to 25OHD levels, data shows that patients undergoing CABG combined with valve surgery had significantly lower 25OHD (10.7 ± 5.4 ng/ml) serum values than isolated CABG patients (14.6 ± 6.51 ng/ml, p = 0.017; Fig. 3B).

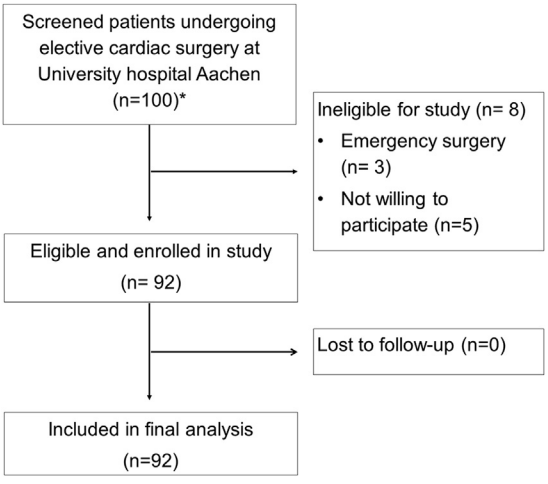

Fig. 1. Flow chart.

3.3. Univariate analysis of postoperative clinical outcome with respect to preoperative 25 OHD levels and $1,25(OH)_2D$ levels

While the odds ratios to develop postoperative organ dysfunction, PCT levels ≥5 μg/l, death, ICU length of stay and hospital length of stay were significant for the active form of vitamin D ($1,25(OH)_2D$) and therefore were further investigated by multivariable-adjusted statistical analysis (Table 3), 25OHD levels showed no significant odds ratios with regard to postoperative organ dysfunctions (p = 0.6019), as can be seen in the ROC curve (Supplemental digital content 3), and has therefore not been further analyzed.

3.4. Multivariable-adjusted statistical analysis of postoperative clinical outcome with respect to preoperative $1,25(OH)_2D$ levels

First, we entered model selection with different sets of baseline parameters. We identified possible important covariates for each binary outcome separately: organ dysfunction, infection and death (Supplemental digital content 4) and chose three separate multivariable models due to the large number of possible important covariates compared to the sample size. The first model considered preoperative illness and demography, the second model considered type of surgery and intraoperative factors and the third one considered preoperative laboratory parameter (Table 3). The multivariable-adjusted statistical analyses revealed that the risk for postoperative organ dysfunction, PCT levels ≥5 μg/l, mortality or prolonged hospital stay is significantly lower for every ng/l increment in $1,25(OH)_2D$ after adjusting for preoperative illness and demography (model 1). Model two shows that after adjusting for the type of surgery $1,25(OH)_2D$ levels do not independently provide information about mortality, while it still does for all other outcomes. Preoperative laboratory parameters seem to play a more important role with regard to postoperative PCT levels and mortality, however it has to be stated that some of these parameters (such as hemoglobin, thrombocytes) will be corrected intraoperatively. For these statistical analyses $1,25(OH)_2D$ levels were not categorized in terms of deficiency vs sufficiency. When using a cut-off of $1,25(OH)_2D$ levels < or ≥20 n/l, data shows that patients with $1,25(OH)_2D$ deficit develop twice as often postoperative organ dysfunctions than patients without a deficit (p = 0.015) (Fig. 4A). Procalcitonin levels on the 2nd postoperative day were also significantly higher in patients with preoperative $1,25(OH)_2D$ deficit vs non-deficit (22.33 vs 3.67 μg/l, p = 0.003) (Fig. 4B).

4. Discussion

In our prospective observational study, 60% of the patients had 25OHD levels under 12 ng/ml and 20% showed $1,25(OH)_2D$ levels <20 ng/l prior to surgery. Börgermann et al. provided first evidence about age related differences in vitamin D levels in patients undergoing cardiac surgery [7]. In extension to these findings, our data significantly expand the current understanding of the role of vitamin D in cardiac surgery patients as blood samples were measured within hours after surgery for a better characterization of its kinetics and our data precisely demonstrates an association between preoperative 1,25(OH)2D levels and postoperative organ dysfunctions (including acute respiratory distress syndrome, acute kidney injury, cardiogenic shock, liver failure, neurologic dysfunction and nosocomial infections), ICU length of stay, hospital length of stay and death, after performing a multivariable-adjusted statistical analysis.

Our study shows a significant intraoperative decrease of $1,25(OH)_2D$ levels among cardiac surgery patients, while serum levels of 25OHD did not significantly change. Baseline $1,25(OH)_2D$

Table 1
Baseline characteristics of cardiac surgery patients (n = 92) by 1,25(OH)2D levels.

Variable	$1,25(OH)_2D \geq 20$ ng/l (N = 74)			$1,25(OH)_2D < 20$ ng/l (N = 18)			p-value
	N	mean	SD	N	mean	SD	
Age (years)	74	67.27	11.11	18	70.06	11.39	0.253
Body mass index (kg/m^2)	74	49.22	8.82	18	48.33	10.67	0.713
GFR (ml/min)	74	78.28	17.75	18	58.71	24.34	**0.004**
Hemoglobin (g/dl)	74	13.59	1.78	18	11.81	1.83	**0.003**
Thrombocytes (1.000/µl)	74	223.09	61.86	18	252.44	116.45	0.314
Leukocytes (1.000/µl)	74	7.54	2.44	18	8.24	2.01	0.265
Creatinine (mg/dl)	74	0.97	0.20	18	1.41	0.73	**0.021**
Creatine kinase (U/L)	74	100.7	69.13	18	59.69	29.81	0.297
Variable	N	n	%	N	N	%	
Sex (female)	74	20	27.3	18	5	27.8	1.000
COPD	74	11	14.9	18	1	5.6	0.449
Diabetes	74	20	27	18	11	61.1	**0.011**
Kidney failure	74	6	8.1	18	7	38.9	**0.003**
Arterial hypertension	74	55	25.7	18	15	8.33	0.547
Nicotine abuse	74	22	29.7	18	7	38.9	0.573
Preoperative dialysis	74	0	0	18	0	0	1.000
Left ventricular ejection fraction	74			18			
>50%		30	40.5		4	22.2	
30–50%		39	52.7		9	50	0.543
<30%		5	6.8		5	27.8	**0.018**

COPD: chronic obstructive pulmonary disease; GFR: glomerular filtration rate; significant values (p < 0.050) are depicted in bold.

Table 2
Operative characteristics of cardiac surgery patients (n = 92) by 1,25(OH)2D levels.

Variable	$1,25(OH)_2D \geq 20$ ng/l (N = 74)			$1,25(OH)_2D < 20$ ng/l (N = 18)			p-value
	N	*n*	*%*	*N*	*n*	*%*	
Surgery type	74			18			
CABG		31	41.9		3	16.7	
Valve surgery		20	27		6	33.3	0.157
CABG + valve surgery		20	27		5	27.8	0.265
LVAD		3	4.1		4	22.2	**0.010**
Variable	N	mean	SD	N	mean	SD	
CPB time (min)	70	124.46	45.38	18	119.17	32.34	0.944
Clamping time (min)	69	84.41	32.99	14	78.36	18.71	0.828

CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass; LVAD: left ventricular assist device; significant values (p < 0.050) are depicted in bold.

levels seem to be of particular importance, as patients without preoperative $1,25(OH)_2D$ deficiency still had sufficient $1,25(OH)_2D$ serum levels 24 h postoperatively, whereas serum levels of patients with preoperative deficiency further decreased intraoperatively, resulting in a severe deficiency after surgery.

Furthermore, we detected an association between the preoperative $1,25(OH)_2D$ status and the planed surgical procedure, reflecting a link between the underlying disease and resulting $1,25(OH)_2D$ status. CABG surgery patients had significantly higher 25OHD levels than patients undergoing valve or combined surgery. In fact, previous studies showed that malnutrition occurs on average three times more often among patients with heart valve diseases than in patients with coronary heart disease [20]. Heart valve diseases are associated with profound haemodynamic alterations and progressive weak physical condition [21], which may have contributed to the shown low 25OHD levels in these patients.

As patients undergoing cardiac surgery are frequently exhibited to a systemic inflammatory response, which may lead to the development of organ dysfunctions, the well-known anti-inflammatory properties of $1,25(OH)_2D$ are of special interest [1,7]. These associations become obvious when focusing on the potential link between $1,25(OH)_2D$ levels and the incidence of postoperative organ dysfunctions and infections. While recent studies could not demonstrate an effect of vitamin D application on mortality or CVD outcomes in healthy patients [22] or patients with advanced chronical heart failure [23], our data received form an acute clinical model shows a close association between low preoperative 1,25(OH)2D levels and postoperative organ dysfunction and mortality. These results indicate that the effect of vitamin D differs significantly when substituting it in chronically ill patients compared to acute critically ill patients who are exposed to an acute systematic inflammatory response.

Next, we investigated the role of the kidney function with respect to $1,25(OH)_2D$ values and outcomes. We identified significantly lower preoperative creatinine as well as GFR levels in patients with $1,25(OH)_2D$ deficiency as can be seen in the baseline characteristics. In chronic kidney disease low levels of calcitriol are due to the loss of 1-alpha hydroxylase in the kidney [11,17]. In addition, low levels of calcitriol are implicated to contribute to an unfavorable activated or unsuppressed renin-angiotensin system (RAS) and RAS activation leads to a suppression of the 1-alpha-hydroxylase and thus may further aggravate a calcitriol deficiency [24]. This circle delivers an explanation relation between preoperative $1,25(OH)_2D$ deficiency due to low kidney function. However, after performing multivariable-adjusted statistical analyses, we saw that $1,25(OH)_2D$ deficiency is independently associated with

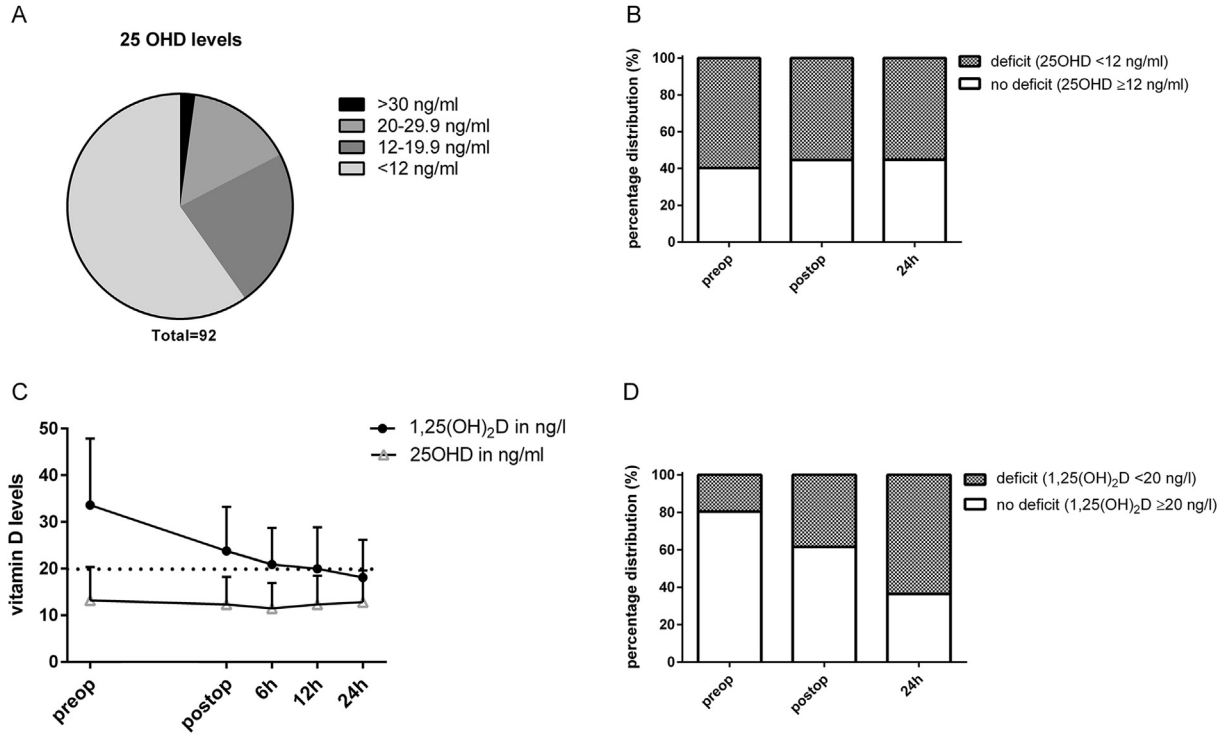

Fig. 2. Distribution of 25 OHD serum levels in cardiac surgery patients (A). Pre-, intra and postoperative time course of serum levels of $1,25(OH)_2D$ and 25OHD in cardiac surgery patients (C). Percentage distribution of patients with or without 25OHD levels ≤12 ng/ml (B) and $1,25(OH)_2D$ levels ≤20 ng/l (D) before and after cardiac surgery. Data represents means +/−, SD; *p < 0.050.

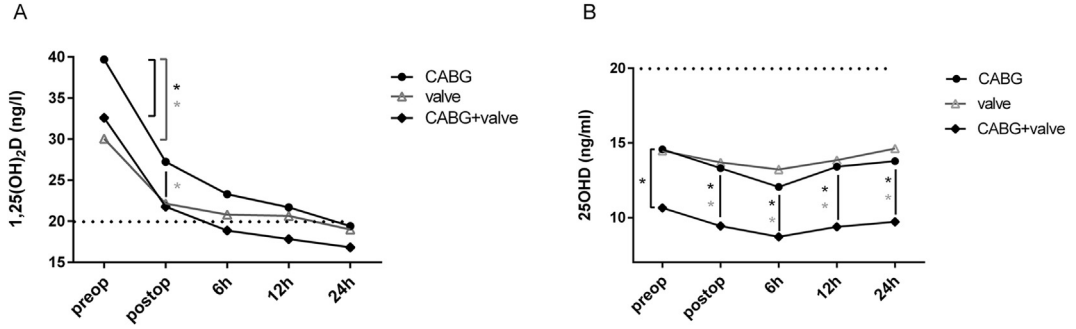

Fig. 3. Association between type of surgery and $1,25(OH)_2D$ (A) and 25OHD (B) levels. Data represents means +/−, SD; *p < 0.050.

Table 3
Univariate (unadjusted) and multivariable-adjusted statistical analyses: change in OR (odds ratio) for every ng/l increment in $1,25(OH)_2D$.

Variable	Univariate analysis		Model 1 (preoperative illness and demographics)		Model 2 (surgery related parameters)		Model 3 (laboratory parameters)	
	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value	OR (CI)	p-value
Organ dysfunction	0.95 (0.92−0.98)	**0.003**	0.95 (0.92−0.99)	**0.009**	0.96 (0.93−1.00)	**0.031**	0.96 (0.92−1.00)	**0.027**
PCT (≥5 μg/l)	0.92 (0.87−0.97)	**0.003**	0.94 (0.88−1.00)	**0.046**	0.92 (0.87−0.98)	**0.007**	0.95 (0.89−1.02)	0.127
Death	0.93 (0.87−0.99)	**0.015**	–	**0.048**[a]	0.95 (0.89−1.00)	0.07	0.96 (0.90−1.02)	0.189
	Mean diff. (CI)	p-value	Mean diff. (CI)	p-value	Mean diff. (CI)	p-value	Mean diff. (CI)	p-value
hospital stay (days)	−0.27 (−0.38−−0.15)	**0.000**	−0.21 (−0.34−−0.09)	**0.001**	−0.21 (−0.34−−0.08)	**0.002**	−0.21 (−0.24−−0.08)	**0.002**
ICU stay (hours)	−2.89 (−4.67−−1.11)	**0.002**	−2.6 (−4.52−−0.68)	**0.009**	−1.99 (−3.94−−0.05)	**0.044**	−2.27 (−4.27−−0.26)	**0.027**

Model 1: **Organ dysfunction/hospital stay/ICU stay:** adjusted for diabetes, ejection fraction, COPD; **PCT > 5 μg/l:** adjusted for diabetes, ejection fraction, kidney failure**; Death:** adjusted for sex, age, BMI, 1,25(OH)D × age; Model 2: **Organ dysfunction/hospital stay/ICU stay:** adjusted for type of surgery, CPB time; **PCT > 5 μg/l:** adjusted for CPB time**; Death:** adjusted for type of surgery; Model 3: **Organ dysfunction/hospital stay/ICU stay:** adjusted for creatinine, hemoglobin, thrombocytes; **PCT > 5 μg/l:** adjusted for creatinine, hemoglobin, creatine kinase**; Death:** GFR, hemoglobin, thrombocytes.

[a] Interaction between death and $1,25(OH_2)$ is clearly significant (p = 0.023) in older patients (≥75 years), but not in younger patients (<75 years) (p = 0.4929).

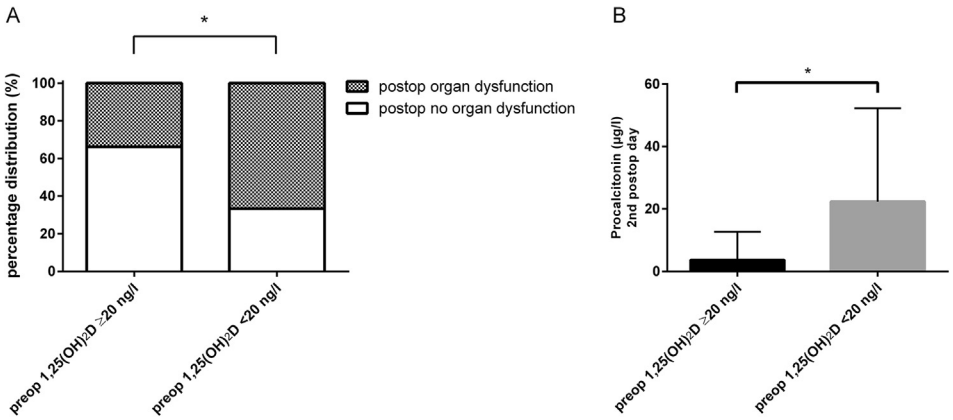

Fig. 4. Percentage of distribution of patients with or without $1,25(OH)_2D$ levels ≤20 ng/l developing postoperative organ dysfunction (A). Procalcitonin levels (µg/l) on 2nd postoperative day in patients with preoperative, postoperative and 24 h postoperative $1,25(OH)_2D$ deficit vs non deficit (B). Data represents means ± SD; *p < 0.050.

worse outcome. Concluding, one can say that the kidney is essential in the synthesis of active vitamin D, but does not independently correlate with outcome while $1,25(OH)_2D$ does.

Taken all these facts together, patients with preoperative vitamin D deficiency (<20 ng/l), are at increased risk to develop postoperative organ dysfunctions, resulting in prolonged hospital stay. This leads to the question whether vitamin D supplementation to these vulnerable patients would result in clinically relevant beneficial effects. In this context, Amrein and colleagues could not show an improvement in clinical outcome (specifically 6-month mortality and LOS) after supplementing high doses of vitamin D3 to a mixed population of critically ill ICU patients with 25OHD levels <12 ng/ml [25]. In a recent meta-analysis, Zittermann and colleagues showed that administration of vitamin $D_{2/3}$ (mean 45 µg/d) lead to an increase of circulating $1,25(OH)_2D$ levels by 12.2 pmol/L (=5.08 ng/l) and activated vitamin D supplementation (mean 0.6 µg/d) created an elevation of 20.5 pmol/L (=8.54 ng/l) in long term follow up patients (mean 321 days) [26]. Given our findings, indicating in the same line that the biological active form $1,25(OH)_2D$ is seemingly of crucial importance for the outcome of cardiac surgery patients, adequately designed studies, which investigate the clinical relevance of a calcitriol supplementation in patients with $1,25(OH)_2D$ deficiency are necessary.

In our exploratory study, we acknowledge several limitations. First, even though patient enrollment and data collection has been assessed prospectively, more information about functional outcome measures and long-term morbidity and mortality are missing. Secondly, cardiac surgery is a very complex intervention where multiple factors, such as intraoperative calcium administration, calcium consumption, blood loss and -management may influence circulating vitamin D levels postoperatively. However, while the influence of fluid administration did not show any influence, the significance of intraoperative given medications such as calcium or potassium remain speculative, whereas it followed our institutional standards. Thirdly, it is known that the length of ICU stay is not only dependent on the physical condition of a patient, but often influenced by lacking capacities by the admitting down-step units. Fourth, until now, it is worth to mention that clear definitions for 25OH deficiencies in critically ill and cardiac surgery patients are still lacking, which may have been useful for justification of the here used cut off values. The high clinical relevance of here investigated values, demonstrate the need to prospectively validate and define such cut offs of clinically relevant 25OH deficiencies for critically ill patients.

Another important widely discussed issue is the measurement of 25OHD. While both the liquid chromatography mass spectrometry (LC-MS/MS) and immunoassays (as used in our study) are useful and reliable methods for measuring 25(OH)D serum-levels in clinical laboratories [27], recent investigations have been conducted to standardize vitamin D measurement and may change future measuring recommendations [28,29].

5. Conclusion

In conclusion, the present multivariable-adjusted statistical analysis highlights that the risk for postoperative organ dysfunction, PCT levels ≥5 µg/l, mortality or prolonged hospital stay is significantly lower for every ng/l increment in $1,25(OH)_2D$ after adjusting for preoperative illness and demography. Following studies are encouraged to clarify whether vitamin D supplementation in cardiac surgery patients with vitamin D deficiency may improve clinical outcome.

Declarations

Ethics approval and consent to participate

The institutional review board (Ethics committee, Medical Faculty, RWTH Aachen University) approved the study. Written informed consent was obtained from all patients prior to data and blood sample collection.

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Statement of authorship

JN together with CS designed the study. CB contributed to the conception of the study and added her methodological expertise to conduct the study. JN and TA carried out data acquisition and blood sample collection. OG analyzed the blood samples with respect to vitamin D. JN, CS and AG analyzed the results and performed statistical analysis together with CF. JN created the graphics. DH, KA, PM, AH and MC included their knowledge in the field of nutrition for data interpretation. JN together with CS drafted the manuscript. DH, KA, PM, MC, GM, CF, AH and OG revised the manuscript and added their valuable expertise to the discussion section. GM and AG provided all needed materials and financial means to conduct the study. All authors added important content to the study and approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work.

Conflict of interest statement

The authors declare that they have no competing interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2018.11.033.

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