Preoperative vitamin D deficiency increases the risk of postoperative cognitive dysfunction: a predefined exploratory sub-analysis

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Conflicts of interest
None declared.

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Clinical trial registration
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Background: Vitamin D is important for maintaining physiological functions including cognition and its deficiency is associated with the occurrence of cognitive impairment. This study was to explore the association between preoperative vitamin D status and the occurrence of postoperative cognitive dysfunction (POCD) in elderly patients undergoing major surgery.
Methods: This was a predefined exploratory sub-analysis of one-centre data from a randomized controlled trial. In all, 123 elderly ($\geq$ 65 years) patients who were scheduled to undergo major cancer surgery were recruited. Serum 25-hydroxyvitamin D concentration was measured before surgery. In total, 59 nonsurgical control subjects with comparable age and education level were also enrolled. A battery of neuropsychological tests was administered the day before and the 7th day after surgery in patients or at the same time interval in control subjects. POCD was diagnosed according to the ISPOCD1 definition.
Results: 71.5% (88/123) of elderly patients had vitamin D deficiency (serum 25-hydroxyvitamin D concentration < 12 ng/ml) before surgery; 24.4% (30/123) of them developed cognitive dysfunction at 1 week after surgery. After adjusting for confounding factors, high preoperative serum 25-hydroxyvitamine D concentration was related to a decreased risk of POCD (odds ratio [OR]: 0.829, 95% confidence interval [CI]: 0.708–0.971; $P = 0.020$), whereas preoperative vitamin D deficiency was associated with an increased risk of POCD (OR: 8.427, 95% CI: 1.595–44.511; $P = 0.012$).
Conclusions: Vitamin D deficiency is prevalent in elderly patients undergoing major cancer surgery and increases the risk of

Editorial comment
In this observational cohort analysis from observations within a larger clinical trial, this study identifies that vitamin D deficiency is common in elderly patients undergoing cancer surgery. They observe an association between this condition with postoperative cognitive dysfunction. This needs to be tested further to identify whether therapy can have an impact on adverse events.

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early POCD development. Whether prophylactic vitamin D supplementation can reduce POCD in the elderly deserves further study.

As one of the fat-soluble vitamins, vitamin D has an important role in maintaining calcium homeostasis and bone health; it is also considered to be involved in maintaining normal cognition and other physiological functions.[1] Vitamin D insufficiency and deficiency are highly prevalent in populations especially in the elderly worldwide.[2–4] Reasons leading to this phenomenon include reduced dietary intake, decreased synthesis within the body, as well as acquired and heritable disorders that interrupt vitamin D metabolism and responsiveness.[1] Vitamin D deficiency increases the occurrence of degenerative bone and joint diseases; furthermore, its deficiency is associated with the occurrence of cognitive impairment[4–8] and the development of diabetes mellitus, hypertension, stroke and even cancer.[9–12]

Human's lifespan is increasing and hence more elderly are receiving surgical therapy. Cognitive decline is a common complication in these patients following surgery, and its occurrence has detrimental effects on both short- and long-term surgical outcomes including mortality, working ability and dependency on social transfer payments.[13] We hypothesized that preoperative vitamin D deficiency might increase the risk of postoperative cognitive dysfunction (POCD). However, current clinical data regarding this relationship are still lacking. The purpose of this study was to explore the association between preoperative serum vitamin D level and the occurrence of POCD in elderly patients undergoing major cancer surgery.

Methods

Study design

This was a predefined exploratory sub-analysis of the one-centre data from a randomized controlled trial which is on-going to compare the impact of sevoflurane-based versus propofol-based general anaesthesia on the incidence of delirium within 7 days in elderly patients after cancer surgery in 17 centres.[14] The study protocol was approved by the Clinical Research Ethics Committee of Peking University First Hospital (2015[869]) on 27 March 2015. Written informed consents were obtained from all subjects or their legal representatives. All patients who were included in the present study were recruited and underwent surgery in Peking University First Hospital. The manuscript adheres to the applicable Equator guidelines (see STROBE checklist).

Patients

The inclusion criteria included the following: (1) age ≥ 65 years and < 90 years; (2) primary cancer without any radio- or chemotherapy and (3) scheduled to undergo elective major surgery for cancer, with an expected duration ≥ 2 h, under general anaesthesia. Patients were excluded if they met any of the following criteria: (1) preoperative history of schizophrenia, epilepsy, Parkinsonism or myasthenia gravis; (2) inability to communicate because of coma, profound dementia, language barrier or end-stage disease in the preoperative period; (3) critical illness (preoperative American Society of Anaesthesiologists physical status classification $\geq$ IV), severe hepatic dysfunction (Child-Pugh class C) or severe renal dysfunction (undergoing dialysis before surgery) or (4) neurosurgery.

A group of control subjects was enrolled from family members or friends of patients with same inclusion and exclusion criteria. They had comparable age and education level as patients but did not receive any surgeries. Their cognition was assessed with neuropsychological tests at the same time interval to quantify the practice effect of repeatedly administered neuropsychological tests.

Data collection

Investigators who were responsible for patient recruitment and data collection were well trained before the study was started. Data collection was performed after obtaining written informed consents. Baseline data included demographic parameters (age, gender, education level, body height and weight), diagnosis, preoperative ASA physical status classification, comorbidities (hypertension, coronary heart disease, diabetes mellitus, chronic obstructive pulmonary disease, stroke, etc.), as well as histories of smoking, drinking and surgery. Blood samples were collected and serum 25-hydroxyvitamin D and calcium concentrations were measured in a clinical laboratory of Peking University First Hospital.

Intraoperative data included type of surgery, durations of anaesthesia and surgery, types and doses of anaesthetic drugs, use of analgesic drugs and glucocorticoids, bispectral index (BIS) value during surgery, and types and volumes of fluid infusion. Postoperative data included the use of analgesics, occurrence of complications within 30 days after surgery, length of stay in hospital after surgery and all-cause 30-day mortality. Postoperative complications were generally defined as newly occur medical conditions that were harmful for patients' recovery and required therapeutic intervention. For patients who were admitted to the intensive care unit (ICU) after surgery, the worst score of Acute Physiology and Chronic Health Evaluation II (APACHE II, scores range from 0 to 71, with higher scores indicating more severe illness) within 24 h, time to extubation (for those who were admitted with endotracheal intubation) and length of ICU stay were also recorded.

Intraoperative data were collected by anaesthesiologists. Baseline data collection and postoperative follow-up were conducted by investigators who were not involved in anaesthesia and perioperative patient care. Anaesthesiologist(s) and investigator(s) had no communication with each other regarding patients' care. Both patients and investigators were blinded to the study group assignment and were unaware of laboratory measurements including serum vitamin D concentrations during the study period.

Neurocognitive assessment

Investigator (GJS) who performed the assessment was specially trained on neuropsychological test administration before the study period. Neuropsychological tests and Mini-Mental State Examination (MMSE) were administered the day before surgery. Paralleled neuropsychological tests were administered at 7th day after surgery. Specific tests included the following: the Mental Control and Digit Span (forward and backward) subtests of the Wechsler Memory Scale; the Visual Retention and Paired Associate Verbal Learning subtests of the Wechsler Memory Scale; the Digit Symbol subtest of the Wechsler Adult Intelligence Scale-Revised; the Halstead-Reitan Trail Making Test (Part A) and the Grooved Pegboard Test (favoured and un-favoured hand). The test battery was recommended by Consensus and had been used in our previous study.[15,16] At 30 days after surgery, cognitive function was assessed by telephone interview with the Chinese version Telephone Interview for Cognitive Status-modified (TICS-m).

POCD was diagnosed according to the International Study of POCD1 definition of which the sensitivity and specificity had been demonstrated.[17,18] To quantify practice effect, baseline scores were compared with 1-week test scores to obtain the average practice effects and their standard deviations (SDs) in control subjects. For patients, baseline scores were compared with 1-week postoperative test scores, subtracted the average practice effects from these changes and divided the results by the control subject SDs to obtain a *Z*-score for each test. The test results were adjusted so that a negative *Z*-score indicated deterioration from the baseline test. The *Z*-scores of all tests in an individual patient were then summarized and divided by the SDs for this sum of *Z*-scores in the control subjects, creating a global *Z*-score. A patient was defined as having POCD when two or more *Z*-scores in individual tests or the combined *Z*-score were −1.96 or less.

Measurement of serum vitamin D concentration

Fasting blood samples were collected in serum separator tubes after obtaining informed consents the day before surgery (or on Friday), and then allowed to clot at room temperature for 0.5–1 h and then placed on ice until centrifugation and serum collection within 4 h. Serum was then stored at −80°C until analysis. The 25-hydroxyvitamine D concentrations were determined by liquid chromatography-mass spectrometry. Preoperative vitamin D status was classified according to the following criteria: adequate, more than 20 ng/ml; insufficient, from 12 to 20 ng/ml; and deficient, < 12 ng/ml.[19]

Statistical analysis

Sample size estimation
According to previous publications, about 69% of Chinese elderly had vitamin D deficiency.[20] We did not find any data regarding the association between preoperative vitamin D level and the occurrence of POCD. In elderly patients, the incidences of early POCD were about 30% (25.8%–41.4%) after major noncardiac surgery[18,21] and 6.8% after minor surgery.[22] We assumed that the incidence of POCD would be the same in patients with or without vitamin D deficiency. With significance set at 0.05 (two-side) and power set at 0.80, the calculated sample size needed to detect the difference was 102 cases. Sample size calculation was performed with the PASS 11.0 software (Stata Corp. LP, College Station, TX, USA).

Outcome analyses
Patients were divided according to the presence of vitamin D deficiency or the development of POCD. Continuous variables with normal distribution were analysed using independent samples *t*-test. Continuous variables with non-normal distribution and ranked data were analysed using Mann–Whitney *U* test. Categorical variables were analysed using the chi-square test, continuity correction chi-squared test or Fisher's exact test. Time-to-event variables were analysed with the Kaplan–Meier estimator, with differences assessed by the Log-Rank test. Univariate Logistic regression analyses were performed to screen factors that were possibly associated with POCD development. Factors with $P < 0.10$ in univariate analyses were included in a multivariate model to determine the association between preoperative vitamin D status and the development of POCD. Two-tailed tests were performed whenever appropriate, and P values of < 0.05 were considered of statistical significance. Outcome analyses were performed with the SPSS 14.0 for Windows (SPSS, Chicago, IL, USA) software package.

Results

Patient recruitment and characteristics

From 1 April 2015 to 30 May 2016, 599 patients were screened for study participation. Of them, 210 were eligible, 123 provided written informed consent and completed the study (Fig. 1, Tables 1 and 2). During the study period, 59 control subjects were enrolled and

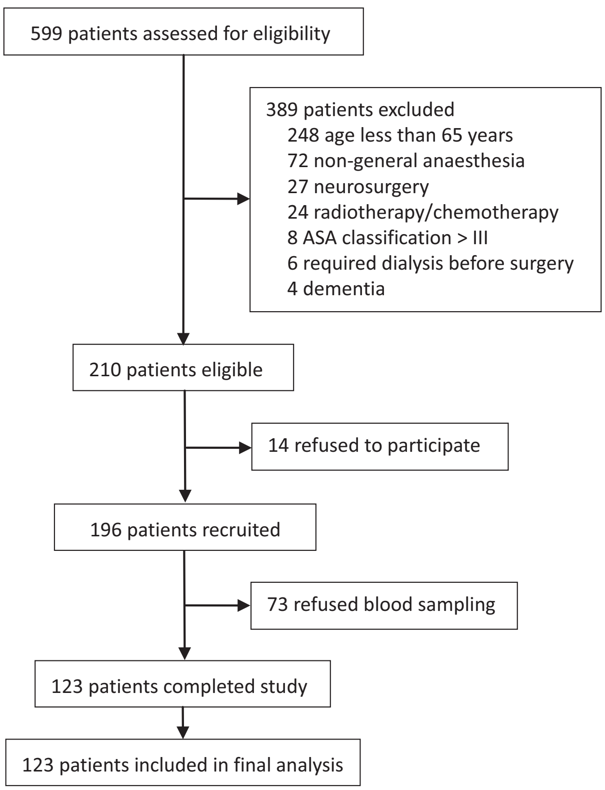

Fig. 1. Flow chart of the study.

Table 1 Demographic and baseline characteristics.

	All patients (*n* = 123)	Vitamin D deficiency* (*n* = 88)	No vitamin D deficiency (*n* = 35)	*P* value	POCD (*n* = 30)	No POCD (*n* = 93)	*P* value
Age, year	73.0 ± 6.0	73.2 ± 6.3	72.2 ± 5.4	0.40	74.6 ± 6.9	72.4 ± 5.7	0.085
Male gender	81 (65.9)	58 (65.9)	23 (65.7)	0.98	22 (73.3)	59 (63.4)	0.32
BMI, kg/m^2	24.0 ± 3.5	24.1 ± 3.5	23.9 ± 3.5	0.81	23.9 ± 3.0	24.1 ± 3.6	0.82
Education, year	10.3 ± 3.5	10.4 ± 3.6	10.0 ± 3.4	0.54	10.1 ± 3.9	10.3 ± 3.4	0.79
ASA classification				0.37			0.70
I	7 (5.7)	4 (4.5)	3 (8.6)		2 (6.7)	5 (5.4)	
II	98 (79.7)	69 (78.4)	29 (82.9)		25 (83.3)	73 (78.5)	
III	18 (14.6)	15 (17.0)	3 (8.6)		3 (10.0)	15 (6.1)	
Preoperative comorbidities							
Stroke	11 (8.9)	6 (6.8)	5 (14.3)	0.29	2 (6.7)	9 (9.7)	0.89
COPD	6 (4.9)	5 (5.7)	1 (2.9)	0.67	2 (6.7)	4 (4.3)	0.63
Chronic smoking†	33 (26.8)	25 (28.4)	8 (22.9)	0.53	14 (46.7)	19 (20.4)	0.005
Coronary heart disease	26 (21.2)	15 (17.0)	11 (31.4)	0.08	7 (23.3)	19 (20.4)	0.74
Hypertension	73 (59.3)	49 (55.7)	24 (68.6)	0.19	15 (50.0)	58 (62.4)	0.23
Diabetes mellitus	29 (23.6)	22 (25.0)	7 (20.0)	0.56	5 (16.7)	24 (25.8)	0.31
Alcoholism‡	15 (12.2)	10 (11.4)	5 (14.3)	0.76	4 (13.3)	11 (11.8)	0.76
History of surgery	59 (48.0)	45 (51.1)	14 (40.0)	0.27	16 (53.3)	43 (46.2)	0.50
1-month weight change, kg	0 (-4, 0)	-1 (-5, 0)	0 (-3, 0)	0.14	-2 (-5, 0)	0 (-4, 0)	0.38
Preoperative MMSE, score	28.3 ± 1.8	28.2 ± 1.7	28.6 ± 1.8	0.28	28.0 ± 1.8	28.5 ± 1.7	0.18
Preoperative serum vitamin D							
Vitamin D concentration, ng/ml§	10.2 ± 4.6	7.9 ± 2.3	16.1 ± 3.6	< 0.001	8.6 ± 4.0	10.7 ± 4.7	0.032
Vitamin D level¶				–			0.032
Adequate	6 (4.9)	–	6 (17.1)		1 (3.3)	5 (5.4)	
Insufficient	29 (23.6)	–	29 (82.9)		2 (6.7)	27 (29.0)	
Deficient	88 (71.5)	88 (100.0)	–		27 (90.0)	61 (65.6)	
Vitamin D deficiency	88 (71.5)	88 (100.0)	–	–	27 (90.0)	61 (65.6)	0.010
Serum calcium concentration, mmol/L	2.26 ± 0.11	2.25 ± 0.11	2.27 ± 0.10	0.36	2.23 ± 0.14	2.27 ± 0.10	0.16

*Defined as serum 25-hydroxyvitamin D concentration < 12 ng/ml. †Smoking of half a pack of cigarettes per day for at least 2 years, either former or current smoker. ‡Daily consumption of the equivalent of 80 g of alcohol for at least 5 years. §Serum 25-hydroxyvitamin D concentration. ¶Defined according to serum 25-hydroxyvitamin D concentration. Adequate: > 20 ng/ml; insufficient: 12–20 ng/ml; deficient: < 12 ng/ml. Data are expressed as mean ± SD, number (%) or median (interquartile range). ASA, American society of anaesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MMSE, mini-mental state examination; POCD, postoperative cognitive dysfunction.

completed both baseline and 1-week follow-up neuropsychological tests. Variables including age ($P = 0.18$), educational level ($P = 0.49$) and time interval to follow-up test ($P = 0.54$) were comparable between patients and control subjects (Table 3).

Of all enrolled patients, 71.5% (88/123) had preoperative vitamin D deficiency and 24.4% (30/123) developed POCD at 1-week after surgery. Compared with patients without vitamin D deficiency, those who had vitamin D deficiency received less sevoflurane ($P = 0.004$), etomidate ($P = 0.003$) and remifentanil ($P = 0.048$) but more propofol ($P = 0.007$) during anaesthesia. Compared with patients without POCD, those who developed POCD had higher percentages of chronic smoking history ($P = 0.005$) and vitamin D deficiency ($P = 0.010$) before surgery; they endured longer anaesthesia and surgery ($P = 0.001$ and 0.002, respectively), lost more blood ($P = 0.001$) and received more fluid infusion ($P = 0.031$) during surgery; they also had higher proportion of ICU admission ($P = 0.006$) and developed more complications within 7 days after surgery ($P < 0.001$; Tables 1 and 2).

Postoperative outcome

Compared with patients without vitamin D deficiency, those with vitamin D deficiency had

Table 2 Perioperative variables.

	All patients (n = 123)	Vitamin D deficiency* (n = 88)	No vitamin D deficiency (n = 35)	P value	POCD (n = 30)	No POCD (n = 93)	P value
Duration of anaesthesia, min	291 (256, 342)	295 (257, 351)	278 (253,319)	0.31	347 (283, 408)	281 (245, 322)	0.001
Duration of surgery, min	206 (178, 262)	207 (179, 267)	203 (172, 232)	0.50	256 (197, 323)	199 (172, 232)	0.002
Intraoperative medication							
Use of sevoflurane†	70 (56.9)	43 (48.9)	27 (77.1)	0.004	21 (70)	49 (52.7)	0.096
Use of propofol	117 (95.1)	87 (98.5)	30 (85.7)	0.007	29 (96.7)	88 (94.6)	>0.99
Propofol, mg‡	150 (75, 796)	523 (80, 540)	100 (50, 499)	0.005	100 (73, 820)	225 (76, 798)	0.36
Use of etomidate	30 (24.4)	15 (17.0)	15 (42.9)	0.003	5 (16.7)	25 (26.9)	0.26
Etomidate, mg‡	12 (10, 15)	10 (10, 14)	12 (10, 16)	0.68	10 (9, 16)	12 (10, 15)	0.50
Use of sufentanil	119 (96.7)	85 (96.6)	34 (97.1)	> 0.99	30 (100)	89 (95.7)	0.57
Sufentanil, μg‡	35 (26, 45)	35 (27, 44)	35 (25, 45)	0.80	39 (34, 45)	35 (25, 45)	0.051
Use of remifentanil	90 (73.2)	60 (68.2)	30 (85.7)	0.048	21 (70.0)	69 (74.2)	0.65
Remifentanil, mg‡	1.4 (0.9, 1.9)	1.4 (0.9, 1.9)	1.4 (1.0, 1.8)	0.37	1.4 (1.1, 2.1)	1.4 (0.9, 1.8)	0.14
Use of dexamethasone	103 (83.7)	74 (84.1)	29 (82.9)	0.87	26 (86.7)	77 (82.8)	0.83
Dexamethasone, mg‡	5.8 ± 1.9	6.0 ± 2.0	5.5 ± 1.6	0.30	6.2 ± 2.1	5.7 ± 1.8	0.30
Intraoperative infusion, ml	2250 (1700, 2850)	1700 (2100, 3075)	2100 (1700, 2600)	0.42	2600 (2100, 3450)	2100 (1600, 2725)	0.031
Estimated blood loss, ml	100 (50, 200)	100 (50, 200)	60 (50, 200)	0.16	200 (95, 425)	60 (50, 200)	0.001
Intraoperative BIS value§	50.2 ± 4.7	49.7 ± 4.8	51.5 ± 4.4	0.07	50.2 ± 4.5	50.2 ± 4.8	0.99
ICU admission after surgery	44 (35.8)	35 (39.7)	9 (25.7)	0.14	17 (56.7)	27 (29.0)	0.006
APACHE II score, score¶	9.7 ± 2.5	8.2 ± 2.7	7.5 ± 2.2	0.13	10.9 ± 2.9	8.9 ± 1.8	0.005
With endotracheal tube¶	24 (19.5)	19 (22.1)	5 (14.3)	0.33	10 (33.3)	14 (15.1)	0.028
Duration of MV, h¶	6.0 (3.6, 8.4)	7.0 (4.9, 5.1)	4.0 (3.0, 5.1)	0.68	8.0 (3.4, 12.6)	4.0 (2.8, 5.2)	0.051
Length of stay in ICU, h¶	20.0 (18.7, 21.3)	21.0 (19.7, 22.3)	19.0 (16.1, 21.9)	0.71	32.0 (10.5, 53.5)	20.0 (18.7, 21.3)	0.42
Postoperative analgesia				0.15			0.64
None	1 (0.8)	1 (1.1)	0		0 (0.0)	1 (1.1)	
PCIA with morphine	75 (61.0)	58 (65.9)	17 (48.6)		20 (66.7)	55 (59.1)	
PCIA with sufentanil	47 (38.2)	29 (33.0)	18 (51.4)		10 (33.3)	37 (39.8)	
Confirmed cancer surgery	113 (91.9)	80 (90.9)	33 (94.3)	0.54	28 (93.3)	85 (91.4)	0.74
Complication within 7 days	15 (12.2)	13 (14.8)	2 (5.7)	0.23	9 (30.0)	6 (6.5)	0.001

*Defined as serum 25-hydroxyvitamin D concentration < 12 ng/ml. †Only used in patients of sevoflurane group in the previous study. ‡Doses of patients who received the drugs. §Average value of BIS monitored at 5 time-points, that is, after anaesthesia induction, before skin incision, 10 min after skin incision, 10 mins after starting tumour resection and before lighting anaesthesia. ¶Results of patients who were admitted to the ICU. Data are expressed as median (interquartile range), number (%), mean ± SD or median (95% confidence interval). APACHE, acute physiology and chronic health evaluation; BIS, bispectral index; ICU, intensive care unit; MV, mechanical ventilation; POCD, postoperative cognitive dysfunction; PCIA, patient-controlled intravenous analgesia.

Table 3 Baseline and follow-up data of control subjects and patients.

	Control subjects (n = 59)	All patients (n = 123)	P value
Age, year	71.9 ± 4.1	73.0 ± 6.0	0.18
Body mass index, kg/m^2	25.1 ± 2.9	24.1 ± 3.5	0.052
Male gender	43 (72.9%)	81 (65.9%)	0.34
Education, year	10.7 ± 4.3	10.3 ± 3.5	0.49
Time interval to follow-up test, day	8.3 ± 1.6	8.1 ± 2.0	0.54
Global *Z*-score, score	−0.03 (−0.61, 0.65)	−0.88 (−1.24, −0.45)	< 0.001
Occurrence of cognitive decline	4 (6.8%)	30 (24.4%)	0.004

Data are expressed as mean ± SD, median (interquartile range) or number (%).

lower global *Z*-score (P = 0.004), developed more POCD at 7th day after surgery (P = 0.010); they had slightly more complications within 30 days (P = 0.060) and slightly lower 30-day TICS-m score (P = 0.066). Compared with patients who did not develop POCD, those who developed POCD had lower global *Z*-score (P < 0.001), longer length of stay in hospital after surgery (P < 0.001), higher incidence of complications within 30 days (P = 0.001) and lower 30-day TICS-m score (P = 0.034; Table 4).

Preoperative vitamin D status and postoperative cognitive dysfunction

Univariate logistic regression analyses showed that either preoperative serum vitamin D (25-hydroxyvitamin D in ng/ml) concentration (ng/ml) or preoperative vitamin D deficiency (serum 25-hydroxyvitamine concentration < 12 ng/ml) was associated with the occurrence of POCD. Univariate analyses also identified nine potential confounding factors (P < 0.10), of which five factors, that is, age, chronic smoking, duration of surgery, use of sevoflurane and complications within 7 days, were included in the multivariate model after testing collinearity. The adjusted results showed that high preoperative serum vitamin D concentration was associated with a decreased risk of POCD (odds ratio [OR]: 0.829, 95% confidence interval [CI]: 0.708–0.971, P = 0.020), whereas preoperative vitamin D deficiency was associated with an increased risk of POCD (OR: 8.427, 95% CI: 1.595–44.511, P = 0.012; Table 5).

Discussion

Our results showed that, in elderly patients who were scheduled to undergo major cancer surgery, 71.5% had preoperative vitamin D deficiency and 24.4% developed POCD at 1 week after surgery. High serum 25-hydroxyvitamin D concentration was associated with a decreased risk of POCD, whereas the presence of preoperative vitamin D deficiency (serum 25-hydroxyvitamin D < 12 ng/ml) was associated with an increased risk of POCD.

Both liquid chromatography-mass spectrometry and enzyme-linked immunosorbent assay are used to measure serum concentration of 25-hydroxyvitamin D; and the adopted normal range of serum 25-hydroxyvitamin D concentration varied in different studies.[6,20,23,24] In the present study, liquid chromatography-mass spectrometry which is more accurate than enzyme-linked immunosorbent assay[25,26] was used and the normal range (adequate: > 20 ng/ml; insufficient: 12–20 ng/ml, deficient: < 12 ng/ml) which is suggested by the Institute of Medicine guidelines was adopted.[19]

Vitamin D deficiency is common in many studied populations.[27] Our results showed that 71.5% of elderly patients had vitamin D deficiency before cancer surgery. This was consistent with the findings on the vitamin D status in the elderly Chinese individuals.[20] It was reported that vitamin D deficiency is associated with accelerated speed of cognitive decline and increased risk of cognitive impairment in the elderly,[6,8,24,28] possibly due to increased production of proinflammatory cytokines, aggregation of β-amyloid peptide and release of inhibitory neurotransmitters in the brain.[29–31] However, controversies exist; for example, vitamin D level was reported to have no correlation with cognitive function in some studies.[23,32,33] Reasons leading to these conflicting results may include

Table 4 Postoperative outcomes.

	Vitamin D deficiency* (*n* = 88)	No vitamin D deficiency* (*n* = 35)	OR, HR, mean difference (95% CI)†	*P* value	POCD (*n* = 30)	No POCD (*n* = 93)	OR, HR, mean difference (95% CI)‡	*P* value
Global Z-score, score	−0.94 (−1.27, −0.54)	−0.54 (−1.02, −0.34)	−0.31 (−0.61, −0.02)	0.017	−1.08 (−1.57, −0.43)	−0.82 (−1.12, −0.45)	−0.26 (−0.57, 0.05)	0.084
7-day POCD	27 (20.7)	3 (8.6)	4.721 (1.330, 16.765)	0.010	30 (100.0)	0 (0.0)	–	–
LOS in hospital, days	9.0 (8.1, 9.9)	9.0 (5.5, 12.5)	1.206 (0.810, 1.795)	0.36	13.0 (7.6, 18.4)	8.0 (7.1, 8.9)	3.412 (2.111, 5.515)	< 0.001
Complications within 30 days	17 (19.3)	2 (5.7)	3.951 (0.862, 18.104)	0.060	13 (43.3)	6 (6.5)	11.088 (3.698, 33.248)	0.001
30-day TICS-m, score	25.5 ± 2.5	26.4 ± 2.4	−0.9 (−1.9, 0.1)	0.066	24.9 ± 2.6	26.0 ± 2.6	−1.1 (−2.1, −0.1)	0.034
All-cause 30-day mortality	0 (0.0)	0 (0.0)	–	–	0 (0.0)	0 (0.0)	–	–

*Defined as serum 25-hydroxyvitamin D concentration < 12 ng/ml. †Calculated as vitamin D deficiency group vs. or minus no vitamin D deficiency group. ‡Calculated as POCD group vs. or minus no POCD group. Data are expressed as median (interquartile range), number (%), median (95% confidence interval) or mean ± SD. HR, hazard ratio; LOS, length of stay; OR, odds ratio; POCD, postoperative cognitive dysfunction; TICS-m, telephone interview for cognitive status-modified.

differences in study populations, ethnicity, area of living, diet, season, colour of skin and others. In the present study, preoperative MMSE score did not differ significantly between patients with or without vitamin D deficiency.

For the diagnosis of POCD, we administered a battery of neuropsychiatric tests that covered domains frequently affected by anaesthesia and surgery such as attention, concentration, figure and visual memory, verbal learning, psychomotor speed, and manual dexterity.[15,16] POCD was diagnosed according to the International Study of POCD1 definition, of which the sensitivity and specificity had been well demonstrated.[17,18] In our study, after adjusting learning effects derived from nonsurgical control subjects due to repeated cognitive assessments, POCD developed in 24.4% of all enrolled patients, similar to previously reported results.[18,34]

Our study found that the risk of 7-day POCD development decreases along with the increasing concentration of serum vitamin D; the presence of preoperative vitamin D deficiency is associated with an increased risk of POCD. To our knowledge, this is the first study that reports the correlation between preoperative vitamin D status and the occurrence of cognitive dysfunction in the elderly early after cancer surgery. Additionally, patients with preoperative vitamin D deficiency had slightly lower cognition score and slightly more complications at 30 days after surgery although statistical significance was not reached. Considering the growing number of elderly undergoing surgery, prospective studies investigating whether prophylactic vitamin D supplementation can improve postoperative cognitive outcome in elderly are urgently needed.

In addition to the preoperative vitamin D status, other factors including age, chronic smoking, use of sevoflurane during anaesthesia, duration of surgery and development of complications within 7 days after surgery were also related to POCD development in our results. These were in line with previous studies.[21,35–39] However, after correction of these confounding factors, preoperative vitamin D concentration or deficiency remained a factor that was significantly associated the development of POCD. Our results also showed that patients who developed POCD had worse postoperative outcomes, that is, they had longer length of

Table 5 Association between preoperative vitamin D status and POCD.

	Univariate analysis		Multivariate analysis*	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Serum vitamin D concentration included				
Age, years	1.060 (0.991, 1.134)	0.09	1.181 (1.062, 1.313)	0.002
Chronic smoking	3.408 (1.418, 8.189)	0.006	5.997 (1.660, 21.666)	0.006
Serum vitamin D, ng/ml†	0.889 (0.796, 0.992)	0.036	0.829 (0.708, 0.971)	0.020
Use of sevoflurane	2.095 (0.869, 5.054)	0.10	5.810 (1.68, 20.359)	0.006
Duration of surgery, min	1.009 (1.003, 1.014)	0.002	1.010 (1.003, 1.017)	0.004
7-day complications	6.214 (1.992, 19.384)	0.002	17.956 (3.755, 85.866)	<0.001
Vitamin D deficiency included				
Age, years	1.060 (0.991, 1.134)	0.09	1.186 (1.061, 1.325)	0.003
Chronic smoking	3.408 (1.418, 8.189)	0.006	5.835 (1.598, 21.304)	0.008
Vitamin D deficiency‡	4.721 (1.330, 16.765)	0.016	8.427 (1.595, 44.511)	0.012
Use of sevoflurane	2.095 (0.869, 5.054)	0.10	6.045 (1.728, 21.151)	0.005
Duration of surgery, min	1.009 (1.003, 1.014)	0.002	1.011 (1.004, 1.019)	0.003
7-day complications	6.214 (1.992, 19.384)	0.002	12.986 (2.815, 58.897)	0.001

*Multivariate Logistic regression analysis was performed using a Backward (Wald) stepwise procedure. †Serum 25-hydroxyvitamin D concentration. ‡Defined as serum 25-hydroxyvitamin D concentration < 12 ng/ml. CI, confidence interval; OR, odds ratio, POCD, postoperative cognitive dysfunction.

hospital stay, higher incidence of complications within 30 days and lower 30-day TICS-m score, thus further demonstrating the harmful effects of POCD development.[13,21]

There are several limitations in the present study. Firstly, as a predefined sub-analysis, the sample size of the study was limited and the number of cases who developed POCD was small. This might result in bias of estimation. Secondly, previous studies found that there was a close relationship between the season of study and the concentration of serum 25-hydroxyvitamin D. Serum vitamin D concentration tends to be lower in winter than in summer.[40] In the present study, the season during which patients were recruited was not included as a confounding factor during analysis. However, the relatively long period of study might have offset this bias in our results. Thirdly, we only observed cognitive outcome at 7 days after surgery and did not perform longer follow-up. Therefore, long-term impact of preoperative vitamin D deficiency remains unknown.

Conclusion

Our results showed that, in elderly patients scheduled to undergo major cancer surgery, 71.5% had preoperative vitamin D deficiency and 24.4% developed cognitive dysfunction at 7 days after surgery. The presence of preoperative vitamin D deficiency was associated with an increased risk of POCD. Considering that the number of elderly who need surgical therapy is growing, prospective studies investigating whether prophylactic vitamin D supplementation can reduce POCD occurrence in elderly are urgently needed.

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Authors' contributions

D. X. W.: Conceived the study.

Y. Z., D. M. and W. D. X.: Designed the study. GJS enrolled patients, collected baseline data and performed neuropsychological tests.

Y. X. Z. and S. J. C.: Participated in anaesthesia and collected intraoperative data.

Y. Z.: Performed postoperative data collection. D. X. W. and Y. Z. analysed and interrupted the data.

S. N. Z. and H. J. L.: Contributed to statistical analyses.

Y. Z.: Drafted the manuscript.

D. M. and D. X. W.: Critically revised the manuscript. D. X. W. is the principal investigator and has overall responsibility for the trial.

All authors read and approved the final manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Occurrence of complications within 7 days after surgery.

Table S2. Occurrence of complications within 30 days after surgery.

Table S3. STROBE Statement—Checklist of items that should be included in reports of cohort studies