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ORIGINAL RESEARCH

Risk Factors for Postoperative Cognitive Decline After Orthopedic Surgery in Elderly Chinese Patients: A Retrospective Cohort Study

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Purpose: We aimed to identify the risk factors for postoperative cognitive decline (POCD) by evaluating the outcomes from preoperative comprehensive geriatric assessment (CGA) and intraoperative anesthetic interventions.

Patients and Methods: Data used in the study were obtained from the Aged Patient Perioperative Longitudinal Evaluation–Multidisciplinary Trial (APPLE-MDT) cohort recruited from the Department of Orthopedics in Xuanwu Hospital, Capital Medical University between March, 2019 and June, 2022. All patients accepted preoperative CGA by the multidisciplinary team using 13 common scales across 15 domains reflecting the multi-organ functions. The variables included demographic data, scales in CGA, comorbidities, laboratory tests and intraoperative anesthetic data. Cognitive function was assessed by Montreal Cognitive Assessment scale within 48 hours after admission and after surgery. Dropping of ≥1 point between the preoperative and postoperative scale was defined as POCD.

Results: We enrolled 119 patients. The median age was 80.00 years [IQR, 77.00, 82.00] and 68 patients (57.1%) were female. Forty-two patients (35.3%) developed POCD. Three cognitive domains including calculation (P = 0.046), recall (P = 0.047) and attention (P = 0.007) were significantly worsened after surgery. Univariate analysis showed that disability of instrumental activity of daily living, incidence rate of postoperative respiratory failure (PRF) ≥4.2%, STOP-Bang scale score, Caprini risk scale score and Sufentanil for maintenance of anesthesia were different between the POCD and non-POCD patients. In the multivariable logistic regression analysis, PRF ≥ 4.2% (odds ratio [OR] = 2.343; 95% confidence interval [CI]: 1.028–5.551; P = 0.046) and Sufentanil for maintenance of anesthesia (OR = 0.260; 95% CI: 0.057–0.859; P = 0.044) was independently associated with POCD as risk and protective factors, respectively.

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Conclusion: Our study suggests that POCD is frequent among older patients undergoing elective orthopedic surgery, in which decline of calculation, recall and attention was predominant. Preoperative comprehensive geriatric assessments are important to identify the high-risk individuals of POCD.

Keywords: cognitive dysfunction, postoperative cognitive complications, orthopedic surgery, comprehensive geriatric assessment, risk factors

Introduction

As the population ages, surgery is being performed frequently in older patients, which was accompanied by high frequency of complications. Postoperative cognitive dysfunction (POCD), a common postoperative complication, is defined as an objective cognitive decline after surgery.[1] Studies have shown that 26% of patients over the age of 65 years had POCD within a few weeks of non-cardiac surgeries.[2] Moreover, previous studies demonstrated that patients with POCD experienced a much higher risk for new disability after surgery, such as impairment of independence in activities of daily living.[3] Due to the increasing incidence of POCD, it is important to identify the risk factors and interventions for POCD. In contrast to POCD, postoperative delirium (POD) occurs in the first few days following surgery which develops no earlier than the end of the first postoperative week. However, POD is considered a strong predictor of POCD development and a harbinger of POCD which has far more significant repercussions on patient health and the healthcare system.[4]

The pathogenesis of POCD is complex and remains poorly understood. Glumac et al reported that preoperative administration of corticosteroids ameliorates the inflammatory response induced by surgery and, thereby, reduce the incidence and severity of POCD, suggesting that inflammatory response has a key role in POCD development.[5] In addition, embolism,[6] hypoperfusion[7] and other factors during the surgery have also been proposed as the potential mechanisms for POCD.

Previous studies have suggested the patient-, operation- anesthesia-specific risk factors. The patient-specific factors include age, educational level, preoperative mental health and chronic pain.[8–10] The operation- and anesthesia-specific factors include duration and complexity of surgery, duration of anesthesia and anesthetic drugs used.[8,11] Although all the studies focused on elderly over 65 years old, the features in even older (≥75 years) patients, who may have more frequent and severe complications, have not been delineated. Moreover, although comprehensive geriatric assessment (CGA) was advocated increasingly for elderly,[12] it has not been specifically applied to screen risk factors for POCD.

The Aged Patient Perioperative Longitudinal Evaluation–Multidisciplinary Trial (APPLE-MDT) cohort recruited the elderly patients over 75 years undergoing elective orthopedic surgery. All enrolled patients accepted CGA before and after surgery, and the cognitive status was assessed using the Montreal Cognitive Assessment (MoCA) scale, which was sensitive and specific to screen cognitive impairment.[13] We hypothesized that preoperative CGA is likely to have a positive impact on identifying the risk factors for POCD in older patients to improve decision-making for the elective surgery and plan for perioperative interventions.

Materials and Methods

The Establishment of the APPLE-MDT Cohort

The protocol of the APPLE-MDT study has been published previously.[14] In brief, this study is a single-center, parallel and randomized study developed to: (1) evaluate the comprehensive risk for surgery based on preoperative multidisciplinary assessments; (2) assist doctors and patients in decision-making for orthopedic surgery with general anesthesia; and (3) formulate managements and interventions to these risk factors. Upon understanding the assessment results and the informed consent, the patients were scheduled for elective orthopedic surgery. Patients were recruited from Department of Orthopedics in Xuanwu hospital, Capital Medical University between March, 2019 and June, 2022. This study was approved by the ethics review board of Xuanwu Hospital of Capital Medical University (2018–086) and registered in Chinese Clinical Trial Registry (ChiCTR1800020363). All patients accepted CGA by multidisciplinary specialists including orthopedists, anesthetists, neurologists, geriatricians, nutritionists, pharmacists and nurses within 48 hours of admission and 48 hours after surgery.

Perioperative CGA Assessment

Data used in this study were obtained from the APPLE-MDT study, and patients with complete data including CGA evaluation, intraoperative data and postoperative MoCA assessment were enrolled. Variables with missing values ≥20% were not included in the study. Definitions of relevant variables were shown in Supplementary Table 1. Briefly, basic personal demographics, comorbidities and laboratory tests were collected from electronic medical record (EMR) which was recorded by orthopedic residents. Preoperative CGA used 13 common scales to assess their state of health across 15 domains covering blood pressure, fasting glucose, fall risk, pain, daily activities, frailty, nutritional status, risk for postoperative respiratory failure (PRF), obstructive sleep apnea (OSA), thrombosis, risk for stroke, scales for anxiety and depression, and the American Society of Anesthesiologists class (ASA) and medications (Supplementary Table 1).

Intraoperative Surgery and Anesthesia

Intraoperative surgical and anesthetic data were collected from the electronic surgical and anesthesia records for the orthopedic operation. All patients underwent spinal fusion surgery with general anesthesia. Spinal localization included cervical, lumbar, cervical and lumbar, and thoracolumbar vertebra. All included patients were prepared for routing general anesthesia by inserting an intravenous line, and electrocardiogram, noninvasive blood pressure, pulse oximetry, and PET CO2 were monitored. Following consideration of perioperative risks, the anesthetist group will implement individualized anesthesia schemes for each patient including full sedation, analgesia, antistress management, accurate monitoring indicator management, objectives-oriented liquid management, and circulation ventilation management, as appropriate. Drugs used in surgery are listed in Supplementary Table 1.

Cognitive Assessment and Definition of POCD

Patients with history of dementia (diagnosed in medical records) who were unable to cooperate with the evaluation were excluded from APPLE-MDT cohort. Pre- and postoperative cognitive assessments were conducted using the MoCA scale by the neurologists. MoCA is a highly sensitive and specific brief cognitive screening tool for detecting cognitive impairment, and < 24 points was defined as cognitive impairment. It evaluates orientation to time and place, executive functions, calculation, naming, repetition, visuospatial function short-term and delayed recall and attention.[15] For correcting the education effects, one point was added for participants with 12 years of education or less on their total MoCA scores (if <30). Drop of ≥1 point between preoperative and postoperative MoCA assessments was defined as the POCD.

Statistical Analysis

The distribution normality of numerical variables was assessed with the two-tailed Shapiro–Wilk and Lilliefors tests. For univariate analysis, we used Mann–Whitney *U*-test for non-normal distributions (data reported as median [interquartile range, IQR]) or the independent samples *t*-test for normally distributed continuous variables (data reported as mean ± standard deviation [SD]), and Chi-Square test for categorical variables (reported as count[%]) to compare differences between POCD and non-POCD groups. For all statistical tests, we chose 0.05 as the significance level. A multivariable logistic regression model was established to screen independent risk factors for predicting POCD. Variables with significant differences in the univariate analysis and risk factors identified in previous studies were included in the stepwise logistic regression analysis model by both forward and backward steps. The algorithm can both add and remove variables in an iterative manner based on the Akaike Information Criterion (AIC). We did not calculate the sample size, but we referred to previous literature[9,16–18] in which sample sizes ranged from 60 to 130, close to our sample size. All analyses were performed using R statistical software version 4.1.1 (R Project for Statistical Computing).

Results

Characteristics of Patients and POCD

We enrolled 119 patients with complete data, including preoperative baseline information and multidisciplinary assessments for surgery and anesthesia and postoperative MoCA score. The characteristics of patients were shown in Table 1.

Table 1 Demographic of Patients with or Without POCD

	Total	Non-POCD group	POCD group	*P* value
N (%)	119	77 (64.7)	42 (35.3)	
Age, years	80.00 [77.00, 82.00]	80.00 [77.00, 82.00]	79.00 [76.25, 81.75]	0. 575
Sex				0.561
Female	68 (57.1)	46 (59.7)	22 (52.4)	
Male	51 (42.9)	31 (40.3)	20 (47.6)	
BMI, kg/m^2	24.67±3.75	24.36±3.70	25.23±3.83	0.228
Residence				0.411
Urban	102 (85.7)	68 (88.3)	34 (81.0)	
Rural	17 (14.3)	9 (11.7)	8 (19.0)	
Education				0.259
Illiteracy	7 (5.9)	5 (6.5)	2 (4.8)	
Primary school	22 (18.5)	11 (14.3)	11 (26.2)	
Middle school or above	90 (75.6)	61 (79.2)	29 (69.0)	
Nationality				0.344
Han	114 (95.8)	75 (97.4)	39 (92.9)	
Other	5 (4.2)	2 (2.6)	3 (7.1)	
Marriage				0.711
Widowed	8 (6.7)	6 (7.8)	2 (4.8)	
Marriage	111 (93.3)	71 (92.2)	40 (95.2)	
Smoke				0.741
Yes	10 (8.4)	6 (7.8)	4 (9.5)	
No	109 (91.6)	71 (92.2)	38 (90.5)	
Drink				0.696
Yes	7 (5.9)	4 (5.2)	3 (7.1)	
No	112 (94.1)	73 (94.8)	39 (92.9)	

Notes: Numerical variables were expressed as the median [IQR] or mean±SD, categorical variables were n (%). Mann–Whitney *U*-test was used for comparing variables with non-normal distributions, independent sample *t*-test was used for normally distributed continuous variables, and Chi-Square test was used for testing differences of categorical variables between POCD and non-POCD patients. P <0.05 was considered as the significant level.

Abbreviations: POCD, postoperative cognitive decline; BMI, body mass index; SD, standard deviation; IQR, interquartile range.

Of these patients, the median age was 80.00 [IQR, 77.00, 82.00] years, 68 (57.1%) were female, and 90 (75.6%) had junior middle school education or above. The highest prevalent comorbidity was hypertension (64.7%), followed by diabetes (27.7%), ischemic heart diseases (23.5%) and anemia (20.2%). Patients with history of anesthesia accounted for 79.8%, and 46.2% patients had general anesthesia before. No significant differences in demographic information, comorbidities and laboratory testing results were observed between patients with POCD and without POCD (Table 1 and Supplementary Table 2).

Two days after surgery, we found MoCA scores declined in 42 (35.3%) patients and about half (n = 20, 47.6%) declined 1 point (Figure 1A). In the eight cognitive domains of MoCA scale, three cognitive domains including calculation (P = 0.046), recall (P = 0.047) and attention (P = 0.007) were significantly decreased after surgery (Figure 1B).

Preoperative CGA and POCD

In the preoperative CGAs, we found a significant difference in the assessments of Instrumental Activity of Daily Living (IADL), risk for PRF, OSA and thrombosis between patients with and without POCD (Table 2). Compared to patients without POCD, those with POCD had higher proportion of disability for IADL before surgery (88.1% vs 70.1%; P = 0.048), although the score of IADL scale showed no significant differences between these cases. Moreover, patients with POCD had higher score of PRF risk scale (23.00 points; IQR, 16.00–23.00) than those without (16.00 points; IQR, 16.00–23.00; P = 0.049), and had increased proportion for PRF > 4.2% (P = 0.033). Furthermore, the median score of STOP-Bang scale was 3.00 points [IQR, 2.00–4.00] in patients with POCD which was higher than those without POCD

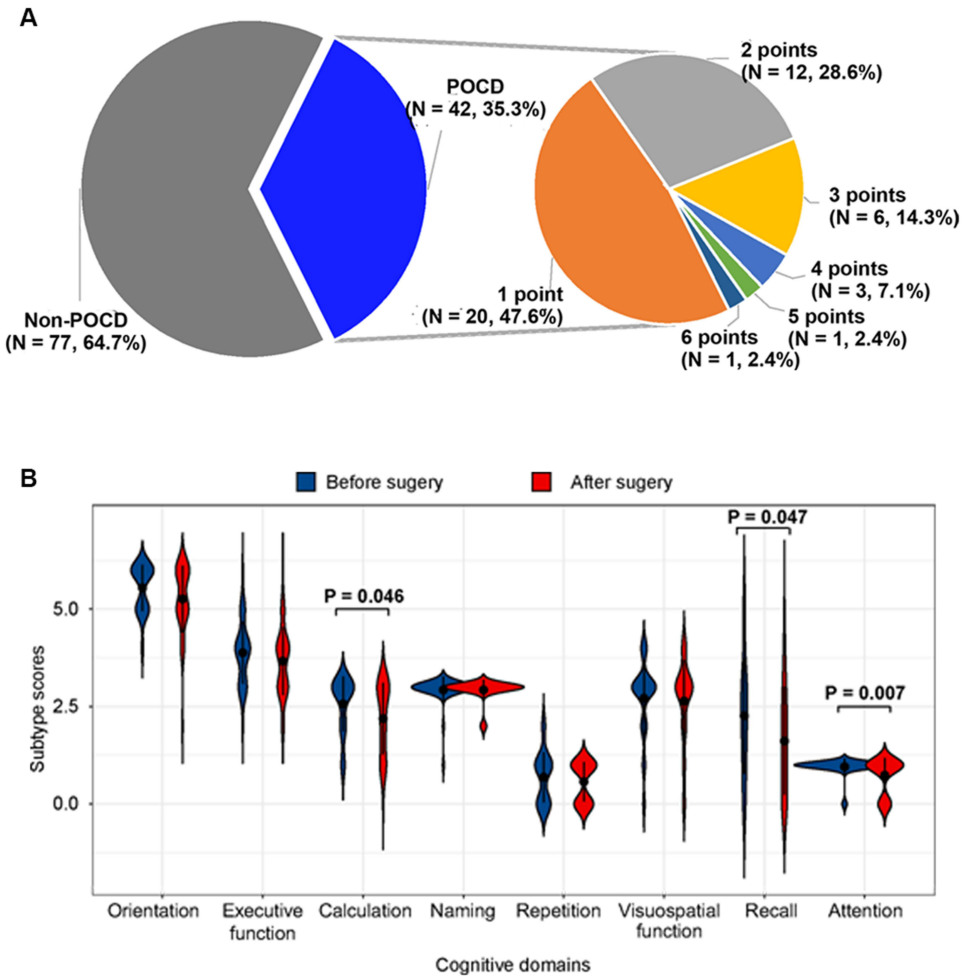

Figure 1 Description of POCD in our cohort. (**A**) Description of POCD in this study. Left pie described the ratio of POCD among all patients (n=119), and right pie described ratio of decreased MoCA points after surgery among POCD group (n=42). (**B**) Comparison of eight cognitive domains before (blue) and after (red) surgery among POCD group (n=42). Black dots and lines inside violin were mean and standard deviation.
Abbreviations: POCD, postoperative cognitive decline.

(2.00 points; IQR, 2.00–3.00; P = 0.026). Although there was no statistical difference, the proportion of high-risk for OSA was higher in POCD patients than non-POCD cases (59.5% vs 44.2%). All patients in the two groups had very high risk for thrombosis, however, patients with POCD had higher score of Caprini risk scale than those without POCD (P = 0.018). Although there was no statistical difference, the proportion of patients with preoperative blood pressure exceeding the surgical criteria was higher in POCD patients than the non-POCD ones (35.7% vs 18.2%, P = 0.057).

Surgical and Anesthetic Variables Associated with POCD

No significant difference in surgical information was observed between the two groups (Table 3). As for anaesthetic delivery, we found only 7.1% patients in POCD group used Sufentanil for maintenance of anesthesia, which was significantly less than the 24.7% of non-POCD group (P = 0.025). Moreover, none of the patients with POCD used Urapidil during surgery, while 9.1% of non-POCD patients used it (P = 0.051).

Multivariable Logistic Regression Analysis

A multivariable logistic regression model was constructed for predicting POCD using age, education, mental health, preoperative cognitive impairment, IADL, incidence rate of PRF, Sufentanil for maintenance of anesthesia and risk for OSA and thrombosis as the covariables. As shown in Table 4, after both selection processes, age, education, mental

Table 2 Preoperative Comprehensive Geriatric Assessments Results of Patients with or Without Cognitive Decline

	Total	Non-POCD Group	POCD Group	*P* value
N (%)	119	77 (64.7)	42 (35.3)	
Score of fall risk scale	11.00 [7.00, 12.00]	11.00 [7.00, 12.00]	10.50 [7.00, 13.00]	0.771
Fall risk				0.645
Low risk	11 (9.2)	7 (9.1)	4 (9.5)	
Moderate risk	90 (75.6)	60 (77.9)	30 (71.4)	
High risk	18 (15.1)	10 (13.0)	8 (19.0)	
VAS				1
No pain	8 (6.7)	5 (6.5)	3 (7.1)	
Pain	111 (93.3)	72 (93.5)	39 (92.9)	
Blood pressure met surgical criteria				0.057
Yes	90 (75.6)	63 (81.8)	27 (64.3)	
No	29 (24.4)	14 (18.2)	15 (35.7)	
Fasting glucose met surgical criteria				1
Yes	114 (95.8)	74 (96.1)	40 (95.2)	
No	5 (4.2)	3 (3.9)	2 (4.8)	
Score of ADL scale	85.00 [75.00, 95.00]	85.00 [75.00, 95.00]	85.00 [70.00, 95.00]	0.591
ADL				0.113
Normal	14 (11.8)	7 (9.1)	7 (16.7)	
Mild disability	77 (64.7)	55 (71.4)	22 (52.4)	
Moderate and severe disability	28 (23.5)	15 (19.5)	13 (31.0)	
Score of IADL scale	5.00 [5.00, 6.00]	5.00 [5.00, 7.00]	5.00 [4.00, 6.00]	0.085
IADL				**0.048**
Normal	28 (23.5)	23 (29.9)	5 (11.9)	
Disability	91 (76.5)	54 (70.1)	37 (88.1)	
Score of frailty scale	3.00 [2.00, 3.00]	3.00 [2.00, 3.00]	3.00 [2.00, 3.00]	0.212
Frailty				0.584
Normal and pre-frailty	45 (37.8)	31 (40.3)	14 (33.3)	
Frailty	74 (62.2)	46 (59.7)	28 (66.7)	
Score of PRF risk scale	23.00 [16.00, 23.00]	16.00 [16.00, 23.00]	23.00 [16.00, 23.00]	**0.049**
Incidence rate of PRF				**0.033**
<4.2%	51 (42.9)	39 (50.6)	12 (28.6)	
≥4.2%	68 (57.1)	38 (49.4)	30 (71.4)	
Score of STOP-Bang scale	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	3.00 [2.00, 4.00]	**0.026**
Risk of OSA				0.158
Low risk	60 (50.4)	43 (55.8)	17 (40.5)	
High risk	59 (49.6)	34 (44.2)	25 (59.5)	
Score of Caprini risk scale	8.00 [8.00, 8.00]	8.00 [8.00, 8.00]	8.00 [8.00, 9.00]	**0.018**
Risk of thrombosis				NA
Low/moderate/high risk group	0 (0.0)	0 (0.0)	0 (0.0)	
Very high-risk group	119 (100.0)	77 (100.0)	42 (100.0)	
Score of MNA scale	25.00 [23.00, 27.00]	25.00 [23.00, 27.00]	25.50 [22.50, 27.00]	0.774
Nutritional status				0.654
Well-nourished	81 (68.1)	54 (70.1)	27 (64.3)	
At risk of malnutrition or malnourished	38 (31.9)	23 (29.9)	15 (35.7)	
Preoperative MoCA score	22.00 [20.00, 24.00]	21.00 [19.00, 24.00]	22.50 [21.00, 24.00]	0.221
Cognitive impairment				0.991
No	41 (34.5)	26 (33.8)	15 (35.7)	
Yes	78 (65.5)	51 (66.2)	27 (64.3)	

(*Continued*)

Table 2 (Continued).

	Total	Non-POCD Group	POCD Group	*P* value
Stroke risk				0.937
Low risk	59 (49.6)	38 (49.4)	21 (50.0)	
Moderate risk	35 (29.4)	22 (28.6)	13 (31.0)	
High risk	25 (21.0)	17 (22.1)	8 (19.0)	
Score of SAS scale	36.25 [33.75, 42.50]	36.25 [32.50, 41.25]	36.88 [35.00, 43.75]	0.339
Score of SDS scale	30.00 [27.50, 33.75]	30.00 [27.50, 36.25]	30.00 [28.75, 33.44]	0.9
Mental health				0.522
Yes	74 (62.2)	50 (64.9)	24 (57.1)	
No	45 (37.8)	27 (35.1)	18 (42.9)	
ASA class				0.634
Class 1	1 (0.8)	1 (1.3)	0 (0.0)	
Class 2	71 (59.7)	48 (62.3)	23 (54.8)	
Class 3	47 (39.5)	28 (36.4)	19 (45.2)	
Drug risk				0.687
Yes	89 (74.8)	59 (76.6)	30 (71.4)	
No	30 (25.2)	18 (23.4)	12 (28.6)	
Polypharmacy				1
Yes	31 (26.1)	20 (26.0)	11 (26.2)	
No	88 (73.9)	57 (74.0)	31 (73.8)	

Notes: Numerical variables were expressed as the median [IQR], categorical variables were n (%). Mann–Whitney *U*-test was used for comparing variables with non-normal distributions, independent sample *t*-test was used for normally distributed continuous variables, and Chi-Square test was used for testing differences of categorical variables between POCD and non-POCD patients. P <0.05 was considered as the significant level and bolded.
Abbreviations: ADL scale, Activity of Daily Living scale; IADL scale, Instrumental Activity of Daily Living scale; VAS, Visual Analogue scale; MNA scale, Mini-Nutritional Assessment scale; PRF, postoperative respiratory failure; OSA, obstructive sleep apnea; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; ASA class, The American Society of Anesthesiologists class.

Table 3 Surgery and Intraoperative Anesthesia of Patients with or Without Cognitive Decline

	Total	Non-POCD Group	POCD Group	*P* value
N (%)	119	77 (64.7)	42 (35.3)	
Surgical information				
Spinal localization				0.941
Cervical spine	16 (13.4)	10 (13.0)	6 (14.3)	
Lumbar	87 (73.1)	57 (74.0)	30 (71.4)	
Cervical spine and lumbar	4 (3.4)	3 (3.9)	1 (2.4)	
Thoracolumbar spine	12 (10.1)	7 (9.1)	5 (11.9)	
Number of spines involved	3.0 [3.0, 4.5]	3.0 [3.0, 4.0]	3.0 [3.0, 4.8]	0.901
Operative time	217.0 [160.5, 287.0]	210.0 [161.0, 267.0]	225.5 [162.0, 311.5]	0.448
Intraoperative blood loss	200.0 [100.0, 475.0]	200.00 [100.0, 450.0]	200.00 [100.0, 475.0]	0.777
Volume of blood transfusion	120.0 [0.0, 500.0]	134.0 [0.0, 500.0]	100.0 [0.0, 500.0]	0.986
Intraoperative urinary volume	1200.0 [800.0, 1800.0]	1000.0 [700.0, 1800.0]	1200.0 [925.0, 1800.0]	0.2
Anaesthetic usage, yes/no				
Drugs for induction of anesthesia				
Propofol	29 (24.4)/90 (75.6)	23 (29.9)/54 (70.1)	6 (14.3)/36 (85.7)	0.095
Etomidate	117 (98.3)/2 (1.7)	75 (97.4)/2 (2.6)	42 (100.0)/0 (0.0)	0.539
Midazolam	9 (7.6)/110 (92.4)	6 (7.8)/71 (92.2)	3 (7.1)/39 (92.9)	1
Remifentanil	28 (23.5)/91 (76.5)	22 (28.6)/55 (71.4)	6 (14.3)/36 (85.7)	0.126
Sufentanil	116 (97.5)/3 (2.5)	75 (97.4)/2 (2.6)	41 (97.6)/1 (2.4)	1
Oxycodone	6 (5.0)/113 (95.0)	4 (5.2)/73 (94.8)	2 (4.8)/40 (95.2)	1
Rocuronium	105 (88.2)/14 (11.8)	66 (85.7)/11 (14.3)	39 (92.9)/3 (7.1)	0.374
Cisatracurium Besylate	14 (11.8)/105 (88.2)	11 (14.3)/66 (85.7)	3 (7.1)/39 (92.9)	0.374

(*Continued*)

Table 3 (Continued).

	Total	Non-POCD Group	POCD Group	*P* value
Drugs for maintenance of anesthesia				
Propofol	118 (99.2)/1 (0.8)	76 (98.7)/1 (1.3)	42 (100.0)/0 (0.0)	1
Dexmedetomidine	107 (89.9)/12 (10.1)	71 (92.2)/6 (7.8)	36 (85.7)/6 (14.3)	0.42
Remifentanil	118 (99.2)/1 (0.8)	76 (98.7)/1 (1.3)	42 (100.0)/0 (0.0)	1
Sufentanil	22 (18.5)/97 (81.5)	19 (24.7)/58 (75.3)	3 (7.1)/39 (92.9)	**0.025**
Rocuronium	46 (38.7)/73 (61.3)	32 (41.6)/45 (58.4)	14 (33.3)/28 (66.7)	0.494
Cisatracurium Besylate	15 (12.6)/104 (87.4)	12 (15.6)/65 (84.4)	3 (7.1)/39 (92.9)	0.252
Sevoflurane	21 (17.6)/98 (82.4)	16 (20.8)/61 (79.2)	5 (11.9)/37 (88.1)	0.315
Vasoactive agents				
Norepinephrine	114 (95.8)/5 (4.2)	73 (94.8)/4 (5.2)	41 (97.6)/1 (2.4)	0.655
Phenylephrine	7 (5.9)/112 (94.1)	6 (7.8)/71 (92.2)	1 (2.4)/41 (97.6)	0.419
Ephedrine	18 (15.1)/ (84.9)	10 (13.0)/67 (87.0)	8 (19.0)/34 (81.0)	0.539
Dopamine	1 (0.8)/118 (99.2)	1 (1.3)/76 (98.7)	0 (0.0)/42 (100.0)	1
Dobutamine	1 (0.8)/118 (99.2)	1 (1.3)/76 (98.7)	0 (0.0)/42 (100.0)	1
Atropine	17 (14.3)/102 (85.7)	13 (16.9)/64 (83.1)	4 (9.5)/38 (90.5)	0.412
Esmolol	5 (4.2)/114 (95.8)	5 (6.5)/72 (93.5)	0 (0.0)/42 (100.0)	0.16
Urapidil	7 (5.9)/112 (94.1)	7 (9.1)/70 (90.9)	0 (0.0)/42 (100.0)	0.051
Nicardipine	1 (0.8)/118 (99.2)	1 (1.3)/76 (98.7)	0 (0.0)/42 (100.0)	1

Notes: Numerical variables were expressed as the median [IQR], categorical variables were n (%).Mann–Whitney *U*-test was used for comparing variables with non-normal distributions, independent sample *t*-test was used for normally distributed continuous variables, and Chi-Square test was used for testing differences of categorical variables between POCD and non-POCD patients. P <0.05 was considered as the significant level and bolded.
Abbreviations: BIS, bispectral index; SD, standard deviation; IQR, interquartile range.

Table 4 Multivariable Logistic Regression Analysis for POCD

	Beta	OR (95% CI)	*P* value
IADL			
Normal	Reference	Reference	–
Disability	0.880	2.411 (0.851–7.934)	0.120
Incidence rate of PRF			
<4.2%	Reference	Reference	–
≥4.2%	0.852	2.343 (1.028–5.551)	0.046
Sufentanil for maintenance of anesthesia			
No	Reference	Reference	–
Yes	−1.348	0.260 (0.057–0.859)	0.044

Notes: Covariates initially entered which did not make final both selection progress were: age, education, mental health, cognitive impairment, risk of OSA, risk of thrombosis. P value <0.05 was the significant level and bolded.
Abbreviations: IADL, Instrumental Activity of Daily Living; PRF, postoperative respiratory failure; OSA, obstructive sleep apnea; OR, odds ratio; CI, confidence interval.

health, preoperative cognitive impairment and risk for OSA and thrombosis were removed from the model. The incidence rate of PRF ≥4.2% was revealed to be independently associated with the POCD (odd ratio [OR] = 2.343; 95% confidence interval [CI]: 1.028–5.551; P = 0.046). In contrast, usage of Sufentanil for maintenance of anesthesia (OR = 0.260; 95% CI: 0.057–0.859; P = 0.044) was identified as a protective factor for POCD.

Discussion

In our study, we found that 35.3% of the super-elderly patients (over 75 years old) receiving orthopedic surgeries had POCD, which mainly influenced the ability of recall, calculation and attention. The results also demonstrated that the

preoperative risk for PRF ≥4.2% was an independent risk factor and Sufentanil for maintenance of anesthesia was a protective factor for POCD. Unlike most previous studies, we focused on patients over 75 years old who accepted the management by the same orthopedic and anesthesia team and reduced the heterogeneity in the study.

The advantage of this study is that all patients enrolled accepted preoperative CGAs by multidisciplinary specialists. Prior study which used the same APPLE-MDT cohort demonstrated that the CGAs process reduced mortality and increases safety in older orthopedic surgery patients.[19] However, it did not uncover whether CGAs process can estimate the risk of cognitive decline after orthopedic surgery in older patients. In this study, we first explored the relationship between preoperative CGAs and POCD. We showed that preoperative estimated incidence rate of PRF ≥4.2% increased the risk of POCD by 2.3 times. PRF is the most serious postoperative pulmonary complications, which is usually evaluated in all types of surgeries (including aortic aneurysm repair and surgeries for thoracic, neurological, abdominal, vascular and neck), albumin < 30 g/L, blood urea nitrogen <30 mg/dL, dependent functional status, chronic obstructive pulmonary disease (COPD) and age.[20] This index reflects dysfunctions in nutrition status, perioperative fluid management, activity and pulmonary function, which are likely to be associated with POCD. Surgical stress and anesthesia lead to changes in respiratory physiology, altering lung volumes, respiratory drive and muscle function.[21] Patients with high PRF risk may suffer from hypoxemia that commonly develops after general anesthesia and can be aggravated by factors such as hypoventilation due to the residual effects of anesthetics, lung edema, laryngospasm and bronchospasm.[22] Previous studies found that lower PCO_2 was associated with better cognitive performance on measures of executive functioning and attention and verbal memory, whereas higher PO_2 values were associated with better performance on the executive functioning and attention measure.[23] Thus, postoperative recall and attention dysfunction may be caused by intraoperative hypoxemia, and risks for POCD can be reduced by correcting the preoperative risk factors and intraoperative preventive strategies for PRF.

The anesthetics have an important influence on postoperative cognitive function. Sufentanil is agonists of opioid receptors with a strong analgesic effect.[24] Although opioid analgesics have been shown to be risk factors for cognitive decline, we found that Sufentanil for maintenance of anesthesia reduced the incidence of POCD. It may have beneficial roles in recovery and analgesic effect. Compared with patients used fentanyl, the MoCA scores were significantly higher and the incidence of POCD was significantly lower among patients used Sufentanil at 1-day post-surgery.[25] The effects of remifentanil and Sufentanil were controversial. A study revealed that patients receiving Sufentanil have reduced analgesic requirements and better cognitive function postoperatively than those who received remifentanil.[26] On the other hand, there was also a study showed that propofol-remifentanil resulted earlier cognitive recovery than Propofol-Sufentanil in patients undergoing supratentorial craniotomy.[27] However, another study found no difference in POCD between Sufentanil and remifentanil.[28] These controversial results may be caused by heterogeneity of each study such as type of surgery, definition of POCD and time of postoperative cognitive assessment. Our finding suggested the protective roles of Sufentanil in POCD, but, due to the relatively small sample size, it is necessary to be verified in random clinical trials.

Other possible risk factors of POCD we found in the univariate analysis included disability of IADL, risk for OSA and thrombosis. Patients with orthopedic disorders had poor IADL because of pain or disability. Previous study demonstrated that poor IADL was associated with postoperative delirium[29] and higher risk of cardiac and respiration complications.[19] Although not reaching the statistical significance, the relationship between preoperative poor IADL and POCD is still worth investigating. Prevalence of OSA was progressively increased with age, which occurs in ≥20% of people over 60 years old.[30] Our study focused on patients over 75 years old and 49.6% of them had high risk for moderate to severe OSA. Furthermore, previous studies found that untreated OSA often leads to decline of cognitive functions including attention, working memory, episodic memory and executive functions, or even leads to permanent brain damage.[31] The possible contribution of thrombosis to POCD was also found in this study. Since the incidence of thrombosis increases greatly with age, patients with high risk of thrombosis may exist immobility, malignant disease, comorbidities and increased levels of coagulation factors, it is highly possible that POCD could be caused by thrombosis.[32]

The association between cognitive reserve and POCD has been widely reported. We included education level as an indicator of cognitive reserve in multivariable logistic regression, although it had no association with POCD in univariate

analysis. However, we did not find the association between education levels and POCD (p=0.259), as shown in Table 1. However, we did not find the association between education levels and POCD (p=0.259, Table 1). The explanations for the lack of such association might be multifold. One might be related to the relatively small sample size we analyzed. Although the rate of patients in POCD group had more primary school education, the difference did not reach statistical significance. The second might be that we did not specifically analyze the difference between POCD and non-POCD patients with high school and higher education, which was reported to affect the risk for POCD.[33] Further studies are warranted using expanded sample sizes and focusing on patients with higher education level.

There are some limitations in our study. Our sample size was relatively small and we only detected factors associated with POCD within 48 hours after surgery, which may not reflect the dynamic cognitive changes within the whole postoperative period. Moreover, although our patients underwent unified general anesthesia, the anesthetist implement individualized anesthesia schemes for each patient according to the results of preoperative CGA and other factors. Thus, cautions must be taken for using these results in clinical practice. With increased sample size and prolonged follow-up of the patients in the APPLE-MDT cohort, the outcomes will be validated for preventing and targeted interventions for POCD in the advanced elderly patients.

Conclusion

In conclusion, our findings showed that 35.3% of patients over 75 years undergoing elective orthopedic surgery aggravate early cognitive function after surgery, mainly including calculation, recall and attention. Preoperative risk of PRF ≥4.2% increases the POCD, while Sufentanil for maintenance of anesthesia protects patients from POCD.

Abbreviations

POCD, postoperative cognitive dysfunction; CGA, comprehensive geriatric assessment; APPLE-MDT, The Aged Patient Perioperative Longitudinal Evaluation-Multidisciplinary Trial; MoCA, Montreal Cognitive Assessment scale; EMR, electronic medical record; PRF, postoperative respiratory failure; OSA, obstructive sleep apnea; ASA, the American Society of Anesthesiologists class; IQR, interquartile range; SD, standard deviation; IADL, Instrumental Activity of Daily Living; OR, odd ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

Data Sharing Statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was approved by the ethics review board of Xuanwu Hospital of Capital Medical University (2018–086) and registered in Chinese Clinical Trial Registry (ChiCTR1800020363). All participants provided written informed consent. All methods were carried out in accordance with relevant guidelines and regulations complied with the Helsinki declaration.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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