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ORIGINAL ARTICLE

The effect of delirium on the association between frailty and postoperative major complications in elderly patients: a mediation analysis

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Abstract

Purpose Both preoperative frailty and postoperative delirium (POD) are associated with higher risk of postoperative complications. But it is unclear if the effect of preoperative frailty on postoperative complications was mediated by POD.

Methods This study was a mediation analysis of a pooled database. Patients aged ≥ 60 years who underwent elective non-cardiac surgery were enrolled. Preoperative frailty was defined as the modified frailty index (mFI) ≥ 0.27. POD was assessed twice daily within the first 3 days using the Confusion Assessment Method (CAM) for patients without intubation and the CAM for intensive care unit (CAM-ICU) for intubated patients. Major complications within postoperative 30 days were screened. Mediation analysis was employed to explore the relationships between frailty, POD, and postoperative complications.

Results A total of 4684 patients were included. The prevalence of frailty was 10.4% (489/4684). In comparison with non-frail patients, frail patients had a higher incidence of POD (12.7% [62/489] vs 6.5% [271/4195], RR = 2.102, 95% CI 1.568–2.819, $P < 0.001$) and more postoperative complications (21.5% [105/489] vs 16.7% [701/4195], RR = 1.363, 95% CI 1.082–1.716, $P = 0.008$). The adjusted total and direct associations between frailty and postoperative complications were 5.8% (adjusted β, 95% CI, 1.8–9.5%; $P < 0.001$) and 5.0% (adjusted β, 95% CI, 1.1–8.7%; $P = 0.004$), respectively. A significant indirect association via POD was observed (adjusted β = 0.8%; 95% CI, 0.3–1.4%; $P < 0.001$), accounting for 13.8% of the total effect.

Conclusion Preoperative frailty is associated with an increased risk of postoperative complications, mediated in part by early POD, in elderly patients following non-cardiac surgery. Given the modest effect size, further research is warranted to confirm these findings.

Keywords Frailty · Postoperative delirium · Postoperative complications · Elder patients · Mediation analysis

Introduction

Aging population is being great challenge to global health in the forthcoming decades. Frailty, the decrement in physical function reservation, is common in elderly patients, especially in those with chronic diseases. In community-dwelling adults, its prevalence ranges from 3.5% to 27% [1]. But up to 50% of surgical patients may suffer preoperative frailty [2–4].

Frailty is highly associated with an increased risk of postoperative complications and may worsen postoperative recovery such as prolonged length of in-hospital stay and decreased quality of life [2–4]. One meta-analysis reported that frail patients were at two times risk of delirium in surgical populations aged 65 years old and above [4]. Frailty was also associated with higher risk of miscellaneous

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complications such as respiratory, renal, vascular, neurological complications and mortality [5–7].

Postoperative delirium (POD) is an acute onset neurocognitive disorder in elder patients after surgery. It is characterized by inattention, consciousness disturbance, and cognitive dysfunction [8]. The pooled incidence of POD was about 19% after elective surgeries and up to 32% after emergency surgeries [8]. Previous studies reported that delirious patients were at increased risk of postoperative complications and mortality [9].

Frailty is a predisposing risk of POD [10, 11]. Recent trials found that frail patients who suffered POD experienced poorer recovery and had a higher risk of mortality than those only having frailty [12]. One mediation analysis showed that the effect of frailty on postoperative 180-day mortality was partially mediated by POD [13]. Most delirious events occurred in postoperative first 3 days which was earlier than the onset time of the other complications. Considering the temporal association between POD and postoperative major complications, we proposed that the effect of frailty on postoperative major complications might be mediated by POD.

This study was designed to analyze the mediation effect of POD between frailty and postoperative major complications in elder patients undergoing non-cardiac major surgery.

Methods

This retrospective cohort study was approved by the Biomedical Research Ethic Committee of Peking University First Hospital (No. 2021–377). Considering that the study was a secondary analysis of a pooled database, informed consents were waived because of no intervention on patients [14–19].

Participants

A pooled database was established with six published studies focusing on POD [14–19]. The primary protocols of them are summarized in Supplemental file 1.

Patients (aged 60 years or above) undergoing elective non-cardiac major surgery were enrolled. In present study, we excluded patients if they met with any of the following criteria: (1) no assessment of preoperative frailty; (2) no record of POD; (3) no record of postoperative major complications; (4) the occurrence time of postoperative complication was earlier than the first episode of delirious event.

Perioperative management

All patients received standard monitoring in the operating room including electrocardiogram, cuff blood pressure, pulse oxygen saturation, and urine output.

Anesthesia was administrated in line with routine practice according to surgery types [14–19]. For example, spinal anesthesia with 2–3 ml 0.5% bupivacaine was performed for lower-limb surgery; general anesthesia was provided for patients receiving thoracic, abdominal, or spinal surgeries; and peripheral nerve block could be used at the discretion of anesthesiologist.

Patient-controlled intravenous or epidural analgesia was provided if necessary. The aim was to keep numeric rating score (NRS, a 0–10 score with higher score for worse pain intensity) ≤ 3.

Data collection

Baseline data included demographics, surgical diagnosis, comorbidities, smoking, drinking, and ASA classification.

Frailty was assessed using modified frailty index (mFI). The mFI comprises 11 comorbidities with a binary score for each item. The risk of frailty is stratified into three levels according to the ratio of cumulative score divided by 11(no-frailty, 0; prefrailty, $0 < \text{mFI} < 0.27$; and frailty, $\text{mFI} \geq 0.27$) [20].

Intraoperative data included the duration of anesthesia and operation, anesthesia type, site of surgery, intraoperative medications, as well as input and output volumes.

Postoperative data included delirium, postoperative major complications, and length of in-hospital stay after surgery.

POD was defined as delirium that occurred during postoperative first 3 days. Patients were assessed twice daily (0600–0800 and 1800–2000) using the Confusion Assessment Method (CAM) for patients without intubation or the CAM for intensive care unit (CAM-ICU) for intubated patients [14–19]. Investigators who performed postoperative follow-up and delirium assessment had been trained by psychiatrists before the original studies. If necessary, the training session was repeated at 6–12 months in some studies [15, 18, 19].

Major complications within postoperative 30 days were screened. Considering the temporal association, we merely included postoperative major complications which occurred after the first episode of delirious event. For non-delirious patients, occurrence of postoperative major complications was recorded without time limitation.

Postoperative major complications were defined as new-onset events that had adverse effect on patient's clinical outcome and needed medical treatment (i.e., Clavien–Dindo classification grade II or above) [21]. The definitions of major complications are listed in Supplemental file 2. Postoperative major complications included the following items: central nervous system (stroke), cardiovascular system (myocardial infarction, new-onset arrhythmia, cardiac failure, deep vein thrombosis and pulmonary embolism), respiratory system (pneumonia, respiratory failure and atelectasis), acute kidney injury, surgery-related complications (intestinal obstruction, anastomotic fistula, gastrointestinal bleeding, unplanned secondary operation), infection (sepsis, surgical related infection), and death.

Primary outcome

Primary outcome was designed to investigate the mediation association between preoperative frailty, POD, and postoperative major complications.

Statistical analysis

Continuous data with normal distribution were presented as mean (standard deviation, SD) and compared by independent sample *t* test; otherwise, data were presented as median (interquartile range, IQR) and compared using Wilcoxon test. Dichotomous data were presented as number (percentage) and compared using Chi-square test or Fisher's exact test. Time-related variables (such the cumulative risk of POD and postoperative major complications) were analyzed using Kaplan–Meier estimator with Log-rank test and Cox proportional hazards model with hazards ratio (HR) and 95% CI.

Patients were divided into two groups according to mFI $\geq$ 0.27 or not. Univariate analysis was used to screen potential risk factors of postoperative complications. Variables with $P < 0.20$ in univariate analyses were entered into multivariable logistic regression model. Model 1 and Model 2 were independently established to examine the preoperative frailty-postoperative major complication and POD-postoperative major complications associations. In model 3, patients were divided into three groups: frail patients with POD, patients without frailty and POD, and patients with either frailty or POD. This model was used to examine if frail patients with POD were at higher risk than others.

The model for mediation analysis was constructed in accordance with the method described Baron and Kenny [22]. The study was primarily designed to investigate how the causal effect of frailty on postoperative complications could be apportioned into an indirect effect (path a and b, mediated by POD) and a direct effect (path c, Fig. 1). We defined indirect effect as the change in expected incidence of postoperative complications when frailty was fixed, but POD changed as if the status of frailty was changed. We defined direct effect as the change in expected incidence of postoperative complications when frailty changed, but POD was artificially fixed. We modeled POD (the mediator) using a logistic regression, with frailty as an independent variable. We modeled the incidence of postoperative complications (the outcome) using a logistic regression with frailty and POD as independent variables. Total, indirect, and direct effects were quantified using the 'mediation' package. The coefficients of indirect effect estimated the strength of the mediated effect of frailty on postoperative complications, which was how much of the increase in complications that occurred as a result of preoperative frailty was attributable to POD. The coefficient of direct effect estimated the strength of frailty on postoperative complications, which was any effect of frailty on complications that was not mediated by POD. The coefficient of total effect was the sum of the direct

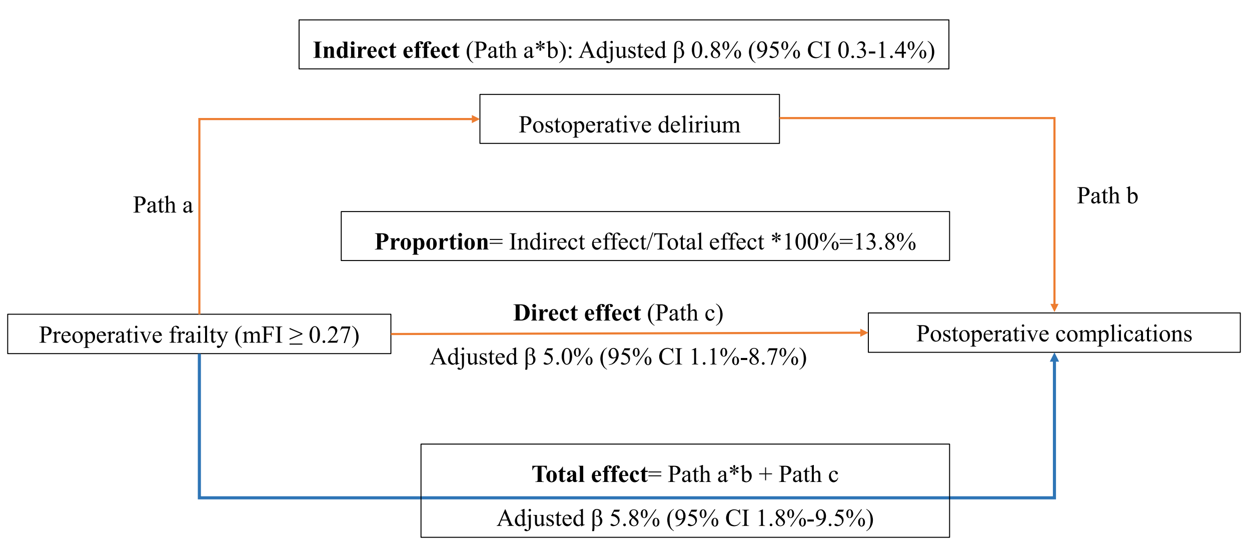

Fig. 1 Mediation analysis. The direct effect of preoperative frailty on postoperative major complications is represented by path c. The effect of the preoperative frailty on the postoperative delirium (POD) is represented by path a; the effect of POD on postoperative major complications is represented by path b. The indirect effect of frailty on postoperative major complications through POD can then be quantified as the product of path a and path b. The total effect is the sum of direct and indirect effects

relationship between preoperative frailty and postoperative complications and the mediated effect through early POD. Bootstrapping (500 iterations) was used to estimate confidence intervals. The procedure was repeated after adjustment for confounders in above multivariable analysis.

Statistical power

The sample size of present study was 4684 patients. We employed the Monte Carlo method to evaluate the statistical power with the R package 'mediation' [23]. With $\alpha = 0.05$, the regression coefficient of frailty (the predictor) on POD (the mediator) = 0.689, stand error (SE) = 0.15, the regression coefficient of POD on postoperative complications (the outcome) = 0.812, SE = 0.13, number of simulations = 10,000, present study yielded a power of 0.956. We further employed the same method to investigate the mediation effects of POD in different subtypes of postoperative complications.

Two-sided $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS 27.0 and R 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria, 2024).

Results

Patients

Among the pooled database of 4832 patients, 4684 of them were included for analysis (Fig. 2). Median age of the enrolled patients was 70 (65, 75) years with mFI of 0.09 (0.00, 0.18). The incidence of frailty was about 10.4% (489/4684).

Compared with control group, frail patients had higher age ($P < 0.001$), less male ($P = 0.004$), higher BMI ($P < 0.001$), higher proportion of comorbidities (such as stroke, hypertension, coronary heart disease, and arrhythmia), less alcohol drinkers ($P < 0.001$), and higher New York Heart Association (NYHA) functional classification ($P < 0.001$) and ASA physical status ($P < 0.001$) (Table 1).

Patients with frailty experienced shorter duration of anesthesia ($P < 0.001$), received more general or regional anesthesia ($P < 0.001$), underwent less thoracic/ abdominal surgery ($P < 0.001$), Table 2. They were given less sevoflurane ($P < 0.001$) and dexmedetomidine ($P = 0.003$) (Table 2). They were taken less fluid input ($P = 0.001$), but with a higher proportion of autologous blood transfusion ($P = 0.040$) (Table 2).

Delirium

The overall incidence of delirium was 7.1% (333/4864). Frail patients suffered higher incidence of POD than those

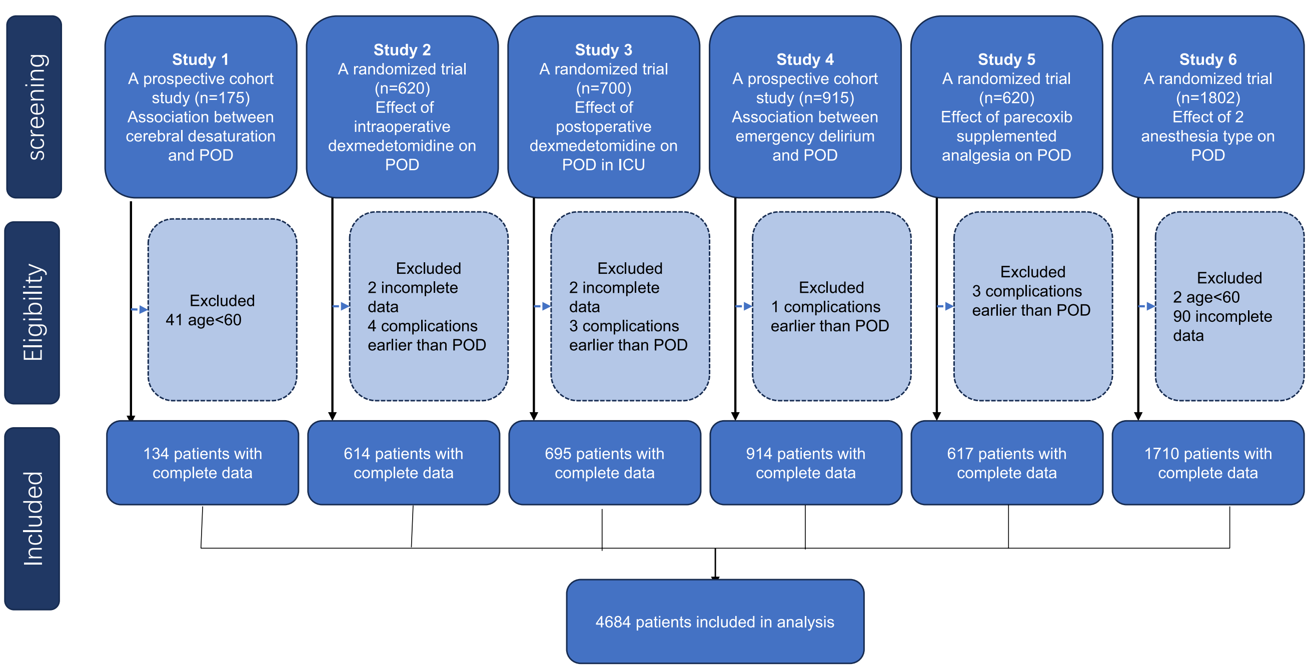

Fig. 2 Flow diagram of the mediation analysis. POD, postoperative delirium

Table 1 Baseline variables

Variables	All patients (*n* = 4684)	Control group (*n* = 4195)	Frailty group (*n* = 489)	*P* value
Age, year	70 (65,75)	69 (65,75)	73 (68, 78)	**< 0.001**
Male, *n* (%)	2684 (57.3)	2434(58.0)	250 (51.1)	**0.004**
Body mass index, kg/m^2	24.11 ± 3.52	24.01 ± 3.49	25.04 ± 3.58	**< 0.001**
Education level, *n* (%)				
Elementary school and illiterate	1325 (28.3)	1180 (28.1)	145 (29.7)	0.060
Middle school	1312 (28.0)	1161 (27.7)	151 (30.9)	
High school	988 (21.1)	887 (21.1)	101 (20.7)	
College	887 (18.9)	810 (19.3)	77 (15.7)	
Graduate school	172 (3.7)	157 (3.7)	15 (3.1)	
ASA classification, *n* (%)				
I	229 (4.9)	229 (5.5)	0 (0.0)	**< 0.001**
II	3667 (78.3)	3407 (81.22)	260 (53.17)	
III	788 (16.8)	559 (13.33)	228 (46.6)	
IV	1 (0.0)	0 (0.0)	1 (0.2)	
NYHA, *n* (%)				
I	3504 (74.8)	3267 (77.9)	237 (48.5)	**< 0.001**
II	1131 (2.6)	899 (21.4)	232 (47.4)	
III	49 (1.0)	29 (0.7)	20 (4.1)	
Preoperative Comorbidities, *n* (%)				
Stroke	431 (9.2)	226 (5.4)	205 (41.9)	**< 0.001**
Hypertension	2234 (47.7)	1763 (42.0)	471 (96.3)	**< 0.001**
Coronary artery disease	679 (14.5)	361 (8.6)	318 (65.0)	**< 0.001**
Arrhythmia[a]	332 (7.1)	279 (6.7)	53 (10.8)	**0.001**
COPD	160 (3.4)	113 (2.7)	47 (9.6)	**< 0.001**
CKD	106 (2.3)	90 (2.1)	16 (3.3)	0.113
Diabetes	968 (20.7)	621 (14.8)	347 (71.0)	**< 0.001**
Chronic smoking[b]	939 (20.0)	842 (20.1)	97 (19.8)	0.902
Drinking[c]	802 (17.1)	748 (17.8)	54 (11.0)	**< 0.001**
Modified frailty index, ratio	0.09 (0.00, 0.18)	0.09 (0.00, 0.09)	0.27 (0.27, 0.27)	**< 0.001**

P-values < 0.05 were bolded to highlight statistically significant results

Data were presented as mean ± standard deviation, median (interquartile range), or number (percentage). *ASA* American Society of Anesthesiologist, *NYHA* New York Heart Association, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease

[a]Including premature ventricular complexes, premature atrial contraction, and I◦ atrioventricular block

[b]Referring to smoking half a pack of cigarettes per day for at least 2 years

[c]Referring to two drinks or more daily, or weekly consumption of the equivalent of 150 mL of alcohol

in control group (12.7% [62/489] vs 6.5% [271/4195], RR = 2.102, 95% CI 1.568–2.819, *P* < 0.001) (Table 2 *and* Supplemental file 3). Kaplan–Meier analysis showed that the cumulative risk of POD was higher in frail patients than control group (Log-rank test *P* < 0.001; Cox risk model HR 1.987, 95% CI 1.501–2.618, *P* < 0.001) (Supplemental file 3). There was no significant difference in the duration of delirium (*P* = 0.146; Table 2).

Postoperative major complications

The overall incidence of postoperative major complications was 17.2% (806/ 4864). Frail patients had higher incidence of postoperative major complications than those in control group (21.5% [105/489] vs 16.7% [701/4195], RR = 1.363, 95% CI 1.082–1.716, *P* = 0.008) (Table 2, Supplemental files 2 and4). Kaplan–Meier analysis showed that the cumulative risk of postoperative major complications was higher in frail patient than control group (Log-rank test *P* = 0.004; Cox risk model HR 1.347, 95% CI 1.097–1.654, *P* = 0.004) (Supplemental file 4).

Risk factors of postoperative major complications

In univariate analysis, 34 variables were analyzed and 24 of them were potentially associated with postoperative

Table 2 Perioperative variables

Variables	All patients (n = 4684)	Control group (n = 4195)	Frailty group (n = 489)	P value
Anesthesia type, n (%)				
General anesthesia (GA)	2603 (55.6)	2307 (55.0)	296 (60.5)	**< 0.001**
Regional anesthesia [a]	617 (13.2)	519 (12.4)	98 (20.0)	
GA + nerve block	1464(31.3)	1369 (32.6)	95 (19.4)	
Duration of anesthesia, hour	4.52 (3.40, 5.93)	4.57 (3.48, 5.95)	4.10 (3.00, 5.63)	**< 0.001**
Site of surgery, n (%)				
Thoracic surgery	961 (20.5)	884 (21.1)	77 (15.7)	**< 0.001**
Abdominal surgery	2733 (58.3)	2477 (59.0)	256 (52.4)	
Orthopedic surgery	900 (19.2)	763 (18.2)	137 (28.0)	
Superficial surgery	90 (1.9)	71 (1.7)	19 (3.9)	
Duration of surgery, hour	3.20 (2.33, 4.43)	3.23 (2.37, 4.48)	2.87 (2.10, 4.15)	**< 0.001**
Intraoperative medications				
Morphine milligram equivalent dose, mg [b]	93.3 (45.0, 166.0)	95.0 (47.0, 170.0)	85.0 (40.0, 147.8	**0.002**
Use of sevoflurane, n (%)	3487 (74.4)	3156 (75.2)	331 (67.7)	**< 0.001**
Use of dexmedetomidine, n (%)	738 (15.8)	684 (16.3)	54 (11.0)	**0.003**
Dexmedetomidine, ug	52(35, 110)	55 (35, 110)	48 (25, 116)	0.163
Total fluid input, mL	2200 (1600, 3100)	2250 (1600, 3100)	2100 (1600, 2850)	**0.001**
Estimated blood loss, mL	100 (50, 300)	100 (50, 300)	100 (50, 300)	0.383
Urine output, mL	500 (300, 500)	500 (300, 500)	500 (250, 550)	**0.001**
Blood transfusion, n (%)[c]	943 (20.1)	831 (19.8)	112 (22.9)	0.106
Autologous blood transfusion, n (%)	470 (10.0)	408 (9.7)	62 (12.7)	**0.040**
Allogeneic blood transfusion, n (%)	561 (12.0)	498 (11.9)	63(12.9)	0.514
Postoperative delirium, n (%)	333 (7.1)	271 (6.5)	62 (12.7)	**< 0.001**
Postoperative first day	233 (5.0)	201 (4.8)	32 (6.5)	0.092
Postoperative Second day	145 (3.1)	109 (2.6)	36 (7.4)	**< 0.001**
Postoperative third day	85 (1.8)	62 (1.5)	23 (4.7)	**< 0.001**
First onset of delirium, day[d]	2.858 (2.842, 2.874)	2.867 (2.851, 2.883)	2.778 (2.721, 2.835)	**< 0.001**
Duration of delirium, day[e]	1.0 (0.5, 1.0)	1.0 (0.5, 1.0)	1.0 (0.5, 1.5)	0.146
Postoperative non-delirium complications, n (%)[f]	806 (17.2)	701 (16.7)	105 (21.5)	**0.008**
Length of in-hospital stay after surgery, day	7 (6,10)	7 (6,10)	7 (6,11)	0.469

P-values < 0.05 were bolded to highlight statistically significant results

Data were presented as number (percentage), median (interquartile range) or median (95% confidence interval)

[a]Including spinal anesthesia, epidural anesthesia or combined

[b]Morphine (i.v.) 10 mg = remifentanil (i.v.) 100 ug = sufentanil (i.v.) 10 ug

[c]Including autologous, allogeneic blood transfusion or both

[d]Referring to first occurrence time of delirium after surgery

[e]Referring to the cumulative duration from first episode to last episode of delirious episode

[f]Referring to the patients suffered postoperative major complications that occurring after postoperative delirium

major complications including frailty (OR 1.363, 95% CI 1.082–1.716, P = 0.008) and POD (OR 2.474, 95% CI 1.938–3.157, P < 0.001), (Supplemental file 5). After adjustment of confounders (variables with P < 0.20 in univariate analysis), both preoperative frailty (model 1) and POD (model 2) were independent risk factors of postoperative major complications, respectively. Model 3 showed that frail patients with delirium had the highest risk of postoperative complications in comparison with those without frailty and POD (Table 3).

Mediation analysis

The total and direct associations between frailty and postoperative complications were 5.8% (adjusted β, 95% CI, 1.8–9.5%; P < 0.001) and 5.0% (adjusted β, 95% CI, 1.1–8.7%, P = 0.004), respectively (Fig. 1 *and* Table 4). The mediation effect of POD on the association between frailty and postoperative major complications was 0.8% (95% CI 0.3–1.4%, P < 0.001), accounting for 13.8% of the total effect (Fig. 1 *and* Table 4).This indicated that

Table 3 Risk factors of postoperative major complications by multivariable logistic regression analysis

Variables	Model 1 for frailty		Model 2 for delirium		Model 3 for frailty with delirium	
	Odds Ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age (per year increase)	1.014 (1.002–1.026)	***0.027***	–	–	–	–
History of coronary heart disease (yes)	–	–	1.259 (1.021–1.553)	**0.031**	–	–
History of chronic kidney disease (yes)	2.069 (1.347–3.177)	**0.001**	1.973 (1.281–3.038)	**0.002**	2.023 (1.315–3.113)	**0.001**
General anesthesia (vs other anesthesia [a])	1.299 (1.105–1.526)	**0.001**	1.278 (1.086–1.503)	**0.003**	1.293 (1.099–1.521)	**0.002**
Anesthesia time (per hour increase)	1.161 (1.118–1.205)	**< 0.001**	1.150 (1.108–1.195)	**< 0.001**	1.154 (1.111–1.198)	**< 0.001**
Thoracic or abdominal surgery (vs other surgery [b])	1.243(0.992–1.558)	0.059	1.259 (1.004–1.580)	**0.046**	1.301 (1.036–1.635)	**0.024**
Allogeneic blood transfusion (yes)	1.597 (1.288–1.981)	**< 0.001**	1.564 (1.258–1.943)	**< 0.001**	1.588 (1.279–1.972)	**< 0.001**
Preoperative frailty (yes) [c]	1.417 (1.115–1.800)	**0.004**	NA	NA	–	–
Postoperative delirium (yes)	NA	NA	2.287 (1.776–2.944)	**< 0.001**	–	–
Patients without frailty and delirium [d]	NA	NA	NA	NA	Ref	Ref
vs. patients with frailty or delirium	NA	NA	NA	NA	1.617 (1.321–1.979)	***< 0.001***
vs. frail patients with delirium	NA	NA	NA	NA	4.022 (2.355–6.869)	***< 0.001***

P-values < 0.05 were bolded to highlight statistically significant results

Ref reference, *NA* not available

[a]Including regional anesthesia (spinal anesthesia, epidural anesthesia or combined) or general anesthesia combined with nerve block /epidural anesthesia

[b]Including orthopedic surgery or superficial surgery

[c]Defined as mFI ≥ 0.27

[d]Patients were divided into three groups including patients without frailty and delirium, patients with frailty or delirium, and frail patients with delirium

Table 4 Total, direct, and indirect association of preoperative frailty with postoperative complications mediated via POD

Model	Total effect		Direct effect		Indirect effect		Proportion mediated
	β (95%CI)	*P* value	β (95%CI)	*P* value	β (95%CI)	*P* value	%
Unadjusted	4.7% (1.1–8.9%)	**0.020**	3.7%(0.2–7.6%)	**0.048**	1.0% (0.4–1.6%)	**< 0.001**	21.3
Adjusted[a]	5.8% (1.8–9.5%)	**< 0.001**	5.0% (1.1–8.7%)	**0.004**	0.8% (0.3–1.4%)	**< 0.001**	13.8

P-values < 0.05 were bolded to highlight statistically significant results

POD postoperative delirium

[a]Adjusted for preoperative chronic kidney disease, anesthesia time, anesthesia type, surgery site and allogeneic blood transfusion

the incidence of postoperative major complication was increased by 0.8% in frail patients who experienced POD.

The first three complications were cardiovascular complications (4.5%), infection complications (3.7%), and pulmonary complications (3.6%). In different subgroups of postoperative major complications, the mediation effects of POD on the frailty-postoperative complications were observed in cardiovascular complications (adjusted β 0.5%, 95% CI, 0.2–1.0%; $P < 0.001$) and infection complications (adjusted β 0.2%, 95% CI, 0.1–0.5%; $P < 0.001$) (Supplemental file 6).

Discussion

Our study showed that both preoperative frailty and POD were associated with an increased risk of postoperative major complications, and only a small percentage of the frailty-complications association was mediated by POD.

The incidence of frailty ranges from 0.5% to 67.2% in different surgical populations [24–27]. Compared with non-oncologic patients, cancer patients have a higher rate of frailty, especially in the older patients [28, 29]. In our study, up to 70% patients received cancer surgery and the incidence of frailty was about 10.4% which was in line with previous report [25].

Frailty is multi-dimensional decrement in functional reservation such as poor activity capacity, malnutrition, and sarcopenia. There were more than 40 definitions of frailty in literatures [30]. The 11 items of mFI mainly included comorbidities such as history of ischemic heart disease and diabetics [31]. These items had long been considered as risk factors of postoperative major complications [32]. The prediction performance of mFI on postoperative complications had been validated by former studies [20, 33]. Thus, this instrument was selected for frailty assessment in this study. Other instruments such as Fried phenotype and Clinical Frailty Scale were also used in perioperative settings, but they mainly focused on functional capacity and nutrition [34, 35]. Indeed, the incidence of frailty might vary greatly in terms of different definitions [34, 35]. Further studies are needed to address the inconsistence of frailty diagnosis.

The pooled incidence of POD in this study was comparable with previous studies [36, 37]. Our study re-confirmed that frailty increased the risk of POD in elder patients. Meanwhile, the duration of POD had no statistical difference between patients with frailty or not. This might be attributed to the shorter duration of POD (about 1 day) in up to 78.7% (262/333) of delirious patients.

To investigate the temporal association, we only included postoperative major complications after the first episode of delirious event. This method had been adopted in previous studies [38]. The first three postoperative major complications were cardiovascular complications, infection complications, and pulmonary complications.

Both frailty and POD had been validated to increase the risk of postoperative complications [9, 39, 40]. We noted that the effect of frailty on postoperative major complications mainly depended on the direct effect. Frail patients were at poor status of functional reservation and they were "vulnerable" to perioperative stress response [27]. The association between POD and postoperative major complications had been reported in many studies and the underlying mechanism might include systematic inflammatory response and organ injury [8].

Our study found that POD partially mediated the effect of frailty on postoperative major complications. Several studies had reported that POD might exacerbate the negative effect of frailty on postoperative complications [12, 13, 41]. However, the casual associations between frailty, POD, and postoperative complications were unclear. Using mediation analysis, our study quantified the effect of POD in the frailty-complications association. To be noted, only a small proportion of the association was mediated by POD. This result indicated that a bundle of strategies to improve frailty (i.e., prehabilitation and nutrition supplement) and prevent delirium (such as dexmedetomidine and multiple modal analgesia) should be considered for perioperative management. A multidiscipline protocol may be more efficient to reduce the risk of postoperative major complications.

Specific mediation effects were observed in frailty-cardiovascular complications and frailty-infection complications. One reason could be attributed to the higher incidence of these complications which yielded sufficient statistical power (i.e., power ≥ 0.8) in mediation analysis. Meanwhile, previous studies had reported that delirium was associated with increased risk of cardiovascular and infection complications [42, 43]. The clinical significance of these findings requires further investigation.

This study had several limitations. Firstly, this study based on a pooled database of six published studies. Although these studies were primarily designed to focus on POD, the discrepancy of inclusion/exclusion criteria might increase the potential bias in participants. We employed univariate and multivariable analyses to adjust potential confounders such as age, comorbidities, and type of surgery and anesthesia. Secondly, a composite of postoperative major complications was used. This was useful to increase the statistical power with a fixed sample size. But we were unable to analyze the mediation analysis for each complication because of their relatively low incidences. Lastly, the scope of this study was confined to the elective non-cardiac surgery population which limited the generalizability of the findings.

Conclusion

This study found that the association between preoperative frailty and postoperative major complications was mediated by POD in elder patients after non-cardiac major surgery. Considering the limited effect size, further investigation is needed to verify the finding.

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Authors' contributions Y-F L: data analysis and manuscript draft. Y-F L, F C, X S, Y-W L, Y Z, C-J L, D-L M: data collection and analysis. C-J L, D-L M: conception and design, manuscript revision and final approval. D-X W: data collection and analysis, critical manuscript revision.

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Data availability This study was a secondary analysis of six datasets, which were available upon reasonable request from the original data providers. Access to these datasets is subject to the respective data-sharing policies and ethical guidelines. Data analysis was performed using SPSS 27.0 and R 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria, 2024). The analytical code has not been publicly shared but is available upon reasonable request from the corresponding author. The datasets used in this study were de-identified and anonymized by the original data providers to ensure compliance with data protection and privacy regulations.

Declarations

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References

1. Dent E, Lien C, Lim WS, Wong WC, Wong CH, Ng TP, Woo J, Dong B, de la Vega S, Poi PJH, Kamaruzzaman SBB, Won C, Chen L, Rockwood K, Arai H, Rodriguez-Mañas L, Cao L, Cesari M, Chan P, Leung E, Landi F, Fried LP, Morley JE, Vellas B, Flickeret L. The Asia-pacific clinical practice guidelines for the management of frailty. J Am Med Dir Assoc. 2017;18(7):564–75.
2. van de Ree CLP, Landers MJF, Kruithof N, de Munter L, Slaets JPJ, Gosens T, et al. Effect of frailty on quality of life in elderly patients after hip fracture: a longitudinal study. BMJ Open. 2019;9(7): e025941.
3. Osaki T, Tatebe S, Orihara J, Uchinaka E, Ashida K, Hirooka Y, et al. Impact of frailty and sarcopenia on short- and long-term outcomes in elderly patients undergoing radical gastrectomy for gastric cancer. World J Surg. 2023;47(12):3250–61.
4. Gracie TJ, Caufield-Noll C, Wang N-Y, Sieber FE. The association of preoperative frailty and postoperative delirium: a meta-analysis. Anesth Analg. 2021;133(2):314–23.
5. Chen D, Ding Y, Zhu W, Fang T, Dong N, Yuan F, et al. Frailty is an independent risk factor for postoperative pulmonary complications in elderly patients undergoing video-assisted thoracoscopic pulmonary resections. Aging Clin Exp Res. 2022;34(4):819–26.
6. George EL, Hall DE, Youk A, Chen R, Kashikar A, Trickey AW, et al. Association between patient frailty and postoperative mortality across multiple noncardiac surgical specialties. JAMA Surg. 2021;156(1): e205152.
7. Gong S, Qian D, Riazi S, Chung F, Englesakis M, Li Q, et al. Association between the frail scale and postoperative complications in older surgical patients: a systematic review and meta-analysis. Anesth Analg. 2023;136(2):251–61.
8. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Aceto P, Audisio R, et al. Update of the european society of anaesthesiology and intensive care medicine evidence-based and consensus-based guideline on postoperative delirium in adult patients. Eur J Anaesthesiol. 2024;41(2):81–108.
9. Yan E, Veitch M, Saripella A, Alhamdah Y, Butris N, Tang-Wai DF, et al. Association between postoperative delirium and adverse outcomes in older surgical patients: a systematic review and meta-analysis. J Clin Anesth. 2023;90: 111221.
10. Ehrlich A, Oh ES, Psoter KJ, Bettick D, Wang NY, Gearhart S, et al. Incidence of post-operative delirium increases as severity of frailty increases. Age Ageing. 2024. https://doi.org/10.1093/ageing/afae168.
11. Bellelli G, Triolo F, Ferrara MC, Deiner SG, Morandi A, Cesari M, et al. Delirium and frailty in older adults: Clinical overlap and biological underpinnings. J Intern Med. 2024;296(5):382–98.
12. Gandossi CM, Zambon A, Ferrara MC, Tassistro E, Castoldi G, Colombo F, et al. Frailty and post-operative delirium influence on functional status in patients with hip fracture: the GIOG 2.0 study. Aging Clin Exp Res. 2023;35(11):2499–506.
13. Pedemonte JC, Sun H, Franco-Garcia E, Zhou C, Heng M, Quraishi SA, et al. Postoperative delirium mediates 180-day mortality in orthopaedic trauma patients. Br J Anaesth. 2021;127(1):102–9.
14. Cui F, Zhao W, Mu D-L, Zhao X, Li X-Y, Wang D-X, et al. Association between cerebral desaturation and postoperative delirium in thoracotomy with one-lung ventilation: a prospective cohort study. Anesth Analg. 2021;133(1):176–86.
15. Li CJ, Wang BJ, Mu DL, Hu J, Guo C, Li XY, et al. Randomized clinical trial of intraoperative dexmedetomidine to prevent delirium in the elderly undergoing major non-cardiac surgery. Br J Surg. 2020;107(2):e123–32.
16. Mu D-L, Zhang D-Z, Wang D-X, Wang G, Li C-J, Meng Z-T, et al. Parecoxib supplementation to morphine analgesia decreases incidence of delirium in elderly patients after hip or knee replacement surgery: a randomized controlled trial. Anesth Analg. 2017;124(6):1992–2000.
17. Su X, Meng Z-T, Wu X-H, Cui F, Li H-L, Wang D-X, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. The Lancet. 2016;388(10054):1893–902.
18. Li Y-W, Li H-J, Li H-J, Zhao B-J, Guo X-Y, Feng Y, et al. Delirium in older patients after combined epidural-general anesthesia or general anesthesia for major surgery: a randomized trial. Anesthesiology. 2021;135(2):218–32.
19. Zhang Y, He S-T, Nie B, Li X-Y, Wang D-X. Emergence delirium is associated with increased postoperative delirium in elderly: a prospective observational study. J Anesth. 2020;34(5):675–87.
20. Velanovich V, Antoine H, Swartz A, Peters D, Rubinfeld I. Accumulating deficits model of frailty and postoperative mortality and morbidity: its application to a national database. J Surg Res. 2013;183(1):104–10.
21. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187–96.
22. Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986;51(6):1173–82.
23. Zhang Z. Monte Carlo based statistical power analysis for mediation models: methods and software. Behav Res Methods. 2014;46(4):1184–98.
24. Wilkes JG, Evans JL, Prato BS, Hess SA, MacGillivray DC, Fitzgerald TL. Frailty cost: economic impact of frailty in the elective surgical patient. J Am Coll Surg. 2019;228(6):861–70.
25. Han B, Li Q, Chen X. Frailty and postoperative complications in older Chinese adults undergoing major thoracic and abdominal surgery. Clin Interv Aging. 2019;14:947–57.
26. Sandini M, Pinotti E, Persico I, Picone D, Bellelli G, Gianotti L. Systematic review and meta-analysis of frailty as a predictor of morbidity and mortality after major abdominal surgery. BJS open. 2017;1(5):128–37.
27. Dhesi JK, Lees NP, Partridge JS. Frailty in the perioperative setting. Clin Med. 2019;19(6):485–9.

28. McIsaac DI, Wong CA, Huang A, Moloo H, Van Walraven C. Derivation and validation of a generalizable preoperative frailty index using population-based health administrative data. Ann Surg. 2019;270(1):102–8.
29. Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, Selby PJ, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2015;26(6):1091–101.
30. McIsaac DI, MacDonald DB, Aucoin SD. Frailty for perioperative clinicians: a narrative review. Anesth Analg. 2020;130(6):1450–60.
31. Shen Y, Hao Q, Wang Y, Chen X, Jiang J, Dong B, et al. The association between preoperative modified frailty index and postoperative complications in Chinese elderly patients with hip fractures. BMC Geriatr. 2021;21(1):370.
32. van Kooten RT, Bahadoer RR, Peeters K, Hoeksema JHL, Steyerberg EW, Hartgrink HH, et al. Preoperative risk factors for major postoperative complications after complex gastrointestinal cancer surgery: a systematic review. Eur J Surg Oncol. 2021;47(12):3049–58.
33. McChesney SL, Canter DJ, Monlezun DJ, Green H, Margolin DA. Modified frailty index predicts postoperative outcomes in patients undergoing radical pelvic surgery. Am Surg. 2020;86(2):95–103.
34. McIsaac DI, Taljaard M, Bryson GL, Beaulé PE, Gagné S, Hamilton G, et al. Frailty as a predictor of death or new disability after surgery: a prospective cohort study. Ann Surg. 2020;271(2):283–9.
35. Arteaga AS, Aguilar LT, González JT, Boza AS, Muñoz-Cruzado VD, Ciuró FP, et al. Impact of frailty in surgical emergencies. a comparison of four frailty scales. Eur J Trauma Emerg Surg Off Publ Eur Traum Soci. 2021. https://doi.org/10.1007/s00068-020-01314-3.
36. Bin Abd Razak HR, Yung WYA. Postoperative delirium in patients undergoing total joint arthroplasty: a systematic review. J Arthroplasty. 2015. https://doi.org/10.1016/j.arth.2015.03.012.
37. Schubert M, Schürch R, Boettger S, Garcia Nuñez D, Schwarz U, Bettex D, et al. A hospital-wide evaluation of delirium prevalence and outcomes in acute care patients - a cohort study. BMC Health Serv Res. 2018;18(1):550.
38. Ma J-H, Liu Y-F, Hong H, Li C-J, Cui F, Mu D-L, et al. Effect of acute pain on the association between preoperative cognitive impairment and postoperative delirium: a secondary analysis of three trials. Br J Anaesth. 2023;130(2):e272–80.
39. McIsaac DI, Bryson GL, van Walraven C. Association of frailty and 1-year postoperative mortality following major elective noncardiac surgery: a population-based cohort study. JAMA Surg. 2016;151(6):538–45.
40. Lin H-S, Watts JN, Peel NM, Hubbard RE. Frailty and post-operative outcomes in older surgical patients: a systematic review. BMC Geriatr. 2016;16(1):157.
41. Sanchez D, Brennan K, Al Sayfe M, Shunker S-A, Bogdanoski T, Hedges S, et al. Frailty, delirium and hospital mortality of older adults admitted to intensive care: the Delirium (Deli) in ICU study. Crit Care. 2020;24(1):609.
42. Kotani T, Ida M, Inoue S, Naito Y, Kawaguchi M. Association between preoperative hand grip strength and postoperative delirium after cardiovascular surgery: a retrospective study. J Clin Med. 2023. https://doi.org/10.3390/jcm12072705.
43. Lee DH, Chang CH, Chang CW, Chen YC, Tai TW. Postoperative delirium in patients receiving hip bipolar hemiarthroplasty for displaced femoral neck fractures: the risk factors and further clinical outcomes. J Arthroplasty. 2023;38(4):737–42.