Review Article

The impact of preoperative frailty on perioperative neurocognitive disorders in elderly patients: A systematic review and meta-analysis

Shan Zhao[1,2], Bei Wang[3], Meinv Liu[1], Dongdong Yu[1], Jianli Li[1]

[1]Department of Anesthesiology, Hebei General Hospital, Shijiazhuang, Hebei, China, [2]Graduate Faculty, North China University of Science and Technology, Tangshan, Hebei, China, [3]Department of Gynaecology, Hebei General Hospital, Shijiazhuang, Hebei, China

Background: Perioperative neurocognitive disorders (PNDs) were the most common complication in elderly patients undergoing surgery. Early identification of risk factors for PNDs and implementation of preventive measures were critical to improve prognosis. We performed this systematic review and meta-analysis to explore the impact of preoperative frailty on PNDs in elderly surgical patients. **Materials and Methods:** Systematic searches were performed in PubMed, Embase, and Web of Science. A fixed-effect model in RevMan5.3 software was conducted due to the low heterogeneity. The potential risk bias was assessed through Funnel plot and Egger's test. Sensitivity analysis was used to examine the robustness of the outcomes. **Results:** Sixteen cohort studies enrolling 4805 elderly patients were qualified for meta-analysis. Pooled results showed that preoperative frailty was linked to the development of PNDs (pooled odds ratio [OR]: 2.40, 95% confidence interval [CI]: 2.05–2.80, $P < 0.001$) without obvious heterogeneity ($P = 0.19$, $I^2 = 22\%$). Subgroup analyses revealed that the correlation between preoperative frailty and PNDs was more remarkable in prospective cohort studies (OR: 3.11, 95% CI: 2.47–3.91, $P < 0.001$) compared to retrospective cohort studies (OR: 1.94, 95% CI: 1.57–2.39, $P < 0.001$; test for subgroup difference, $P = 0.003$). In addition, the correlation in patients with cardiac surgery (OR: 3.38, 95% CI: 2.44–4.68, $P < 0.001$) was more noticeable than noncardiac surgery (OR: 2.17, 95% CI: 1.82–2.59, $P < 0.001$; test for subgroup difference $P = 0.02$). **Conclusion:** Our results demonstrated that preoperative frailty was independently associated with PNDs in geriatric patients undergoing elective surgery.

Key words: Aged, frailty, meta-analysis, postoperative cognitive complications, systematic review

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INTRODUCTION

Perioperative neurocognitive disorders (PNDs), a group of neurocognitive abnormalities associated with anesthesia and surgery, encompassed postoperative delirium (POD), delayed neurocognitive recovery (DNR), and postoperative neurocognitive disorder (NCD).[1] The incidence of PNDs ranged from 9% to 41% in general population, while it occurred up to 65% in older individuals.[2,3] PNDs could lead to adverse results, including prolonged hospitalization, unexpected complications, increased mortality, as well as worsen abilities of daily living and long-term cognitive function, which resulted in increased medical costs and decreased quality of patient's life.[4,5] Unfortunately, the mechanisms underlying the pathogenesis of PNDs remained elusive, which hindered the effective treatment for cognitive disorders.[2] Therefore, preoperative identification and intervention for underlying risk factors of PNDs in elderly patients were crucial.

Recently, considerable studies pointed out that advanced age, preoperative cognitive impairment, operating time, anemia, and inappropriate depth of anesthesia were associated with PNDs.[6-8] Frailty as a common geriatric syndrome was considered a predisposing factor for POD in the European Society of Anesthesiology Guidelines.[9] Frailty was a clinical state of decreased physical reserve

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Address for correspondence: Dr. Jianli Li, Department of Anesthesiology, Hebei General Hospital, Shijiazhuang, Hebei 050051, China.
E-mail: hblijianli@163.com

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and increased vulnerability to stressors due to accumulative declines of multiple physiological functions.[10] The incidence of frailty reportedly claimed to range from 25% to 40% in older patients undergoing major surgery.[11] Frailty conferred a higher risk of negative postoperative outcomes such as fall, hospitalization, disability, and death.[12] Besides, several studies demonstrated that preoperative frailty might be related to an increase of PNDs.[13,14] However, the current understanding of the impact of preoperative frailty on PNDs was insufficient, which needed further evidence. Therefore, we performed a meta-analysis of cohort studies with multivariate analysis to evaluate the relationship of preoperative frailty and PNDs in elderly patients.

METHODS

The meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15] The protocol was registered with PROSPERO (CRD42023448906).

Search strategies

The databases searched for all articles included PubMed, Embase, and Web of Science. An expert researcher conducted the search without language restriction from inception to February 20, 2023. The search strategy was based on combinations of Medical Subject Heading terms and text words. Titles and abstracts were searched from the following four tiers. The keywords in the first tier included frail elderly, frailty and frail. The keywords in the second tier: cognitive dysfunction, delirium, neurocognitive disorders, neurocognitive impairment, cognitive impairment, cognitive decline, neurological complications, cognitive complications, dementia, delirious, acute confusional syndrome, acute confusional, POD, POCD, and deliri*. The keywords in the third tier included postoperative, operation*, surgery, anaesthesia, anesthesia, perioperati*, postoperati*, surg*, and operati*. The keywords in the fourth tier included prospective studies, retrospective studies, cohort studies, observational study, retrospective*, prospective*, cohort stud*, and observational*. In addition, we conducted a manual search of references cited in related review articles to identify additional literatures. The full search strategy through all databases was available in Supplementary Tables 1 and 2.

Inclusion and exclusion criteria

The eligible inclusion criteria were as follows: (1) explored the relationship of preoperative frailty and PNDs; (2) assessed frailty before surgery using validated measurement tools; (3) assessed PNDs using validated international scales except chart review because of the high false-negative rates;[16] (4) patients with a mean age of 65 years or older following elective surgery; and (5) reported odds ratios (ORs) of the relationship of preoperative frailty and PNDs after adjusting potential confounding factors.

Exclusion criteria included the following: (1) review articles, letters, conference abstracts, or case reports and (2) no explicit definition of frailty or PNDs.

Quality evaluation and data extraction

Two authors of this meta-analysis independently reviewed titles and abstracts of the retrieved studies. Different opinions of the study selection were resolved by consensus. The quality of selected studies was assessed using the Newcastle–Ottawa Scale (NOS), ranged from 1 to 9 points and each study was judged on 8 items consisting of three aspects: study group selection, comparability of the groups, and exposure assessment and outcome evaluation.[17] Studies with NOS score ≥7 were considered high quality, and NOS score <7 was defined as low quality. The extracted data included name of the first author, publication year, location of the study, study design, sample size, and the number of males; mean age; type of surgery; frailty measurements; the number of frail patients at baseline; evaluation instruments for the diagnosis of PNDs; the number of patients who developed PNDs; follow-up duration; adjusted ORs and 95% confidence intervals (CIs); and confounding variables adjusted in the multivariate analysis.

Outcome measurements and statistical analysis

Adjusted ORs and their corresponding 95% CIs were calculated to estimate the association between preoperative frailty and PNDs in elderly patients following elective surgery. The heterogeneity among the selected studies was assessed using Cochrane's Q-test and I^2 statistics. A fixed-effect model or a random-effect model was employed to calculate the pooled ORs. When the included studies demonstrated low heterogeneity, a fixed-effect model was applied, whereas a random-effect model was used for studies with moderate to high heterogeneity. Subgroup analyses were conducted to evaluate the impact of study characteristics on the correlation between preoperative frailty and PNDs, including study design, location of study, sample size, gender, cardiac and noncardiac surgeries, as well as evaluation tools of frailty and PNDs. Furthermore, we conducted a sensitive analysis by removing one single study successively to examine the effect of each individual study on the overall effect and the robustness of the outcomes. The potential publication bias in the meta-analysis was assessed through the visual inspection of the symmetry of the funnel plot, as well as the Egger's regression test. If publication bias existed, trim-and-fill analysis was used to adjust the effect of publication bias and further evaluate the stability of the pooled results. We used RevMan 5.3 (Cochrane Collaboration, Copenhagen, Denmark) and STATA (Stata

corporation, Texas, USA) 16.0 software to conduct statistical analyses. For all analyses, statistical significance was set at $P < 0.05$ and 95% CIs were presented.

RESULTS

Search results

Initially, 1728 articles were identified through systematic search via three electronic databases. Two studies were searched manually from related review articles. Subsequently, 1059 articles remained after excluding duplications. 953 studies were excluded by screening the titles and abstracts due to unrelated to the purpose of the meta-analysis. Following the initial screening, we reviewed the full text of 106 studies. Among these, 90 studies were removed due to the following reasons: univariate analysis or inadequate outcome data (34 studies); nonelective setting (9 studies); mean age below 65 years old (5 studies); did not report or fail to measure frailty with a validated scale (11 studies); did not report or fail to assess PNDs with a validated tool (9 studies); no complete study design (e.g., review articles, letters, conference abstracts, or case reports) (21 studies); and repeated report of the same cohort (1 study). Thus, 16 cohort studies fulfilled the eligibility criteria for the meta-analysis. The flow diagram of searching process is shown in Figure 1.

Study characteristics and quality evaluation

Publication dates of the included studies spanned from 2011 to 2022. Overall, our systematic review comprised 4805 patients with an average age varied from 70.1 to 82.3 years old, of which 39.7% were male. Six studies were Asian[14,18-22] and 10 were non-Asian.[23-32] Among these studies, 6 studies were retrospective,[19,20,22,24,28,32] while the other 10 studies were prospective.[14,18,21,23,25-27,29-31] Six studies included patients undergoing cardiac surgeries,[20,22,26,27,30,31] and the other 10 studies included patients following noncardiac surgeries.[14,18,19,21,23-25,28,29,32] The FRAIL Scale, the Edmonton Frail Scale, the Modified Frailty index, and the Fried Frailty Scale were applied to assess frailty, and the prevalence of preoperative frailty in included studies varied from 13.3% to 54.1%. Confusion Assessment Method (CAM), the 4A's Test, Intensive Care Delirium Screening Checklist (ICDSC), and Diagnostic and Statistical Manual of Mental Disorders (DSM)-V were used to diagnose PNDs among the selected studies, and POD was detected in 602 patients, 95 patients were identified as DNR and 10 patients were identified as postoperative NCD. The potential confounding variables, such as age, gender, body mass index, education, and comorbidities, were adjusted in the multivariate analyses to determine the relationship of preoperative frailty and PNDs. The characteristics of the selected studies are reported in Table 1. The NOS scores of

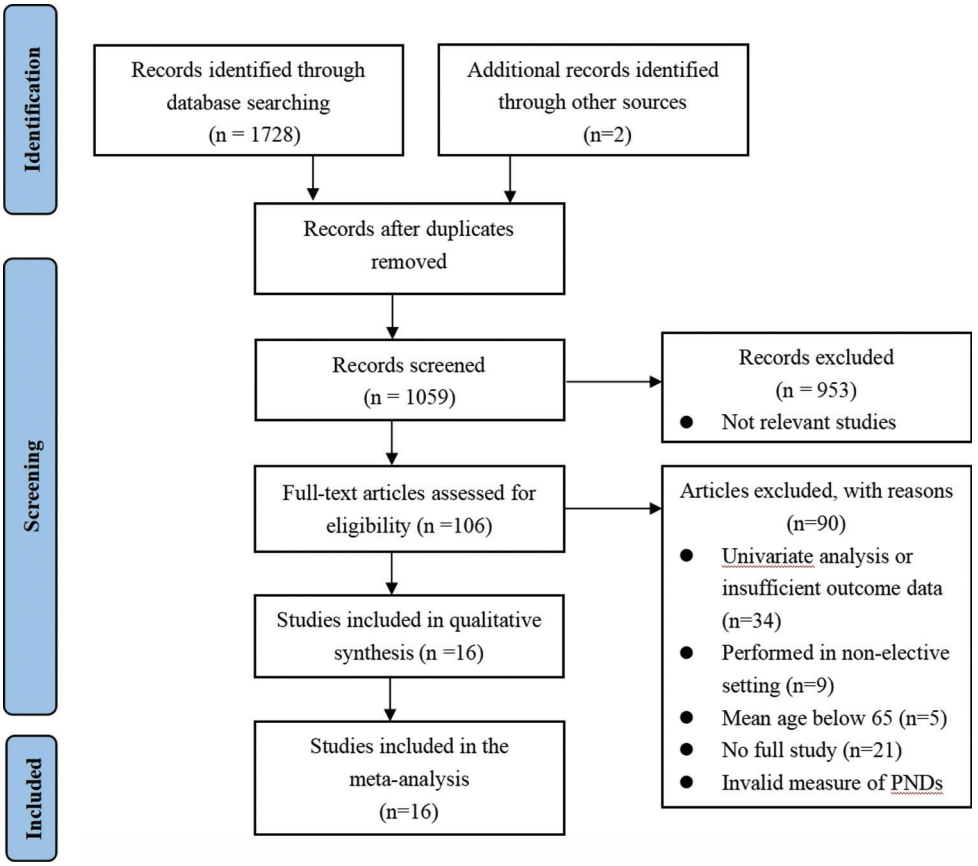

Figure 1: Flow diagram of database search and study selection

Table 1: Characteristics of the included studies

Study (year)	Location	Study design	Sample size	Mean age	Male, *n* (%)	Type of surgery	Frailty measurement	Frailty (*n*)	PNDs measurement	PNDs (*n*)	Follow-up duration	AOR (95%CI)	Adjusted variables
Leung *et al.* (2011)[24]	The US	RC	63	72.3	34 (53.97)	General, arthroplasty, spine, thoracic	Fried Frailty Scale	21	CAM	POD 16	2 days after surgery	1.84 (1.07–3.15)	Age, ADL dependence, IADL dependence, TICS score, GDS score and preoperative depression score
Pol *et al.* (2011)[25]	The Netherlands	PC	142	68.0	100 (70.42)	Vascular surgery	Groningen frailty indicator	50	DOS	POD 10	7 days after surgery	1.9 (0.9–3.7)	Age, CRP, ASA, comorbidities and impaired renal function
Jung *et al.* (2015)[26]	Canada	PC	133	71.0	98 (73.68)	Cardiac surgery	Modified fried criteria	72	CAM	POD 24	Until discharge	5.05 (1.58–16.13)	EuroSCORE II
Nomura *et al.* (2019) [27]	The US	PC	133	72.0	97 (72.93)	Cardiac surgery	Fried Frailty Scale	44	CAM	POD 56	Until discharge	6.31 (1.18–33.74)	Age, sex, education and EuroSCORE
Goudzwaard *et al.* (2020)[30]	The Netherlands	PC	543	79.1	297 (54.7)	TAVI	Erasmus frailty score	95	DSM- IV	POD 75	4 days after surgery	2.37 (1.12–5.07)	Age, prior stroke, renal dysfunction, gait speed, general anesthesia, nontransfemoral access and procedural time
Itagaki *et al.* (2020)[22]	Japan	RC	89	74.9	57 (64.04)	Cardiac surgery	Japanese version of the cardiovascular health study criteria	34	ICDSC	POD 25	Until discharge	4.524 (1.651–12.391)	Age, mild cognitive impairment, sex, albumin and operation type
Mahanna *et al.* (2020)[29]	The US	PC	167	71.0	75 (44.91)	Noncardiac surgery	Frail Scale	31	CAM-ICU	POD 38	Until discharge	2.7 (1.0–7.3)	Age, sex, education, surgical duration, surgical type, ASA and baseline cognitive score
Roopsawang *et al.*(2020)[21]	Thailand	PC	200	72.0	44 (22)	Orthopedic surgery	Edmonton Frail Scale	46	4AT-Test	POD 25	Until discharge	3.52 (1.09–12.26)	Age, sex, type of surgery and comorbidities
Susano *et al.* (2020)[23]	The US	PC	219	75.0	124 (56.62)	Spine surgery	Frail Scale	53	CAM	POD 55	Until discharge	6.6 (1.96–21.9)	Age, BMI, ASA, metabolic equivalent of task, total number of medications, preoperative use of opioids, mini-cog score, animal fluency test score and invasiveness of surgical procedure
Evered *et al.* (2020)[28]	Aulstralia	RC	300	70.1	103 (34.33)	Hip joint replacement	Edmonton Frail Scale	40	RCI, IADLs, subjective cognitive assessment	3 months NCD 5; 12 months NCD 5	3 months after surgery; 12 months after surgery	1.5 (1.02–2.23); 2.0 (1.26–3.17)	Estimated IQ, smoking, hypertension, history of acute myocardial infarction and diabetes
Chen *et al.* (2021)[14]	China	PC	383	72.7	132 (34.46)	Total joint orthroplasty	Modified frailty index	207	DSM- V	POD 66;DNR 95	7 days after surgery; 1 month after surgery	3.31 (1.91–5.72); 2.64 (1.39–3.87)	Age, duration of anesthesia; Age, CRP and preoperative MMSE

Contd...

Table 1: Contd...

Study (year)	Location	Study design	Sample size	Mean age	Male, *n* (%)	Type of surgery	Frailty measurement	Frailty (*n*)	PNDs measurement	PNDs (*n*)	Follow-up duration	AOR (95%CI)	Adjusted variables
Mauri *et al.* (2021)[31]	The US	PC	661	82.3	322 (48.71)	TAVR	Essential frailty toolset	199	CAM-ICU	POD 66	7 days after surgery	4.31 (2.37–7.87)	Sex, atrial fibrillation, pneumonia, stroke, vascular complication and general anesthesia
Ogata *et al.* (2022)[20]	Japan	RC	877	NA	22 (2.51)	TAVI	Frailty index	NR	CAM-ICU	POD 31	Until discharge	2.49 (1.37–4.54)	EuroSCORE, NYHA, GFR and echocardiographic measures
Sieber *et al.* (2022)[32]	The US	RC	324	73.3	196 (60.49)	Elective surgery	Edmonton Frail Scale	83	4AT-Test	POD 15	Until discharge	3.49 (1.06–11.54)	Age, ASA and Elixhauser 30 day readmission score
Tsai *et al.* (2022)[18]	Taiwan	PC	345	NA	206 (59.71)	Cancer surgery	Comprehensive geriatric assessment	186	CAM	POD 19	Until discharge	2.87 (1.05–8.91)	Age, cancer type, operative method, operative time and intraoperative blood loss
Xiang *et al.* (2022)[19]	China	RC	226	70.6	0	Gynecologic cancer surgery	Modified frailty index	31	DSM-V	POD 39	7 days after surgery	1.82 (1.06–3.13)	Age, CCI, SII, CRP, AFR, preoperative anxiety, duration of operation and length of hospital stay

RC=Retrospective cohort; PC=Prospective cohort; NA=Not available; TAVI=Transcatheter aortic valve implantation; TAVR=Transcatheter aortic valve replacement; CAM=Confusion assessment method; CAM-ICU=Confusion assessment model for intensive care unit; DSM-IV=Diagnostic and statistical manual of mental disorders, fourth edition; DSM-V=DSM, fifth edition; DOS=Delirium observation score; ICDSC=Intensive care delirium screening checklist; 4AT-Test=Arousal, attention, abbreviated mental test-4, acute change; RCI=Reliable change index; IADL=Instrumental activities of daily living; ADL=Activities of daily living; TICS=Telephone interview for cognitive; GDS=The Geriatric Depression Scale; MMSE=Mini-mental state examination; CRP=C-reactive protein; ASA=American Society of Anesthesiologists; CCI=Charlson Comorbidity Index; EuroSCORE II=European System for Cardiac Operative Risk Evaluation II; BMI=Body mass index; IQ=Intelligence quotient; SII=Systemic immuneinflammation index; NYHA=New York Heart Association; GFR=Glomerular filtration rate; AFR=Albumin-fibrinogen ratio; PNDs=Perioperative neurocognitive disorders; POD=Postoperative delirium; AOR=Adjusted odds ratio; CI=Confidence interval

the selected studies ranged from 6 to 9 points, indicating moderate to good study quality. Table 2 presents the scoring details of the NOS.

Main results of meta-analysis

Meta-analysis of 16 included studies demonstrated a significant relationship between preoperative frailty and PNDs (pooled OR: 2.40, 95% CI: 2.05–2.80, $P < 0.001$), and no remarkable heterogeneity was observed among the selected studies [$P = 0.19$, $I^2 = 22\%$; Figure 2]. A fixed-effect model was conducted due to the low heterogeneity among studies. Fifteen studies investigated the association of preoperative frailty with POD, and the merged results suggested that preoperative frailty was correlated with POD [OR: 2.76, 95% CI: 2.26–3.36, $P < 0.001$; $I^2 = 0\%$; Figure 3]. Two studies reported the significant association of preoperative frailty with DNR or postoperative NCD [OR: 2.64, 95% CI: 1.66–4.20, $P < 0.001$; OR: 1.69, 95% CI: 1.26–2.27, $P < 0.001$; $I^2 = 0\%$; Figure 3].

Table 2: Quality assessment based on Newcastle-Ottawa Scale

Literature	Selection criteria (/4)	Comparability (/2)	Expose (/3)	Total (/9)
Leung *et al*. (2011)[24]	3	1	2	6
Pol *et al*. (2011)[25]	4	0	3	7
Jung *et al*. (2015)[26]	4	1	3	8
Nomura *et al*. (2019)[27]	4	2	3	9
Goudzwaard *et al*. (2020)[30]	4	1	3	8
Itagaki *et al*. (2020)[22]	4	2	3	9
Mahanna *et al*. (2020)[29]	3	1	3	7
Roopsawang *et al*. (2020) [21]	4	1	3	8
Susano *et al*. (2020)[23]	4	1	3	8
Evered *et al*. (2020)[28]	4	2	1	7
Chen *et al*. (2021)[14]	4	2	3	9
Mauri *et al*. (2021)[31]	4	1	2	7
Ogata *et al*. (2022)[20]	3	1	3	7
Sieber *et al*. (2022)[32]	3	1	3	7
Tsai *et al*. (2022)[18]	4	2	3	9
xiang *et al*. (2022)[19]	4	1	3	8

Results of subgroup analyses

Our subgroup analyses suggested that the association between preoperative frailty and PNDs was not significantly affected by study design, location of study, sample size, gender, cardiac and noncardiac surgeries, as well as evaluation tools of frailty and PNDs [P all > 0.05; Figures 4-6]. Noticeably, we found a more significant relationship of preoperative frailty and PNDs in prospective cohort studies (OR: 3.11, 95% CI: 2.47–3.91, $P < 0.001$) compared to retrospective cohort studies [OR: 1.94, 95% CI: 1.57–2.39, $P < 0.001$; test for subgroup difference $P = 0.003$; Figure 4]. In addition, patients following cardiac surgery (OR: 3.38, 95% CI: 2.44–4.68, $P < 0.001$) were more remarkable than patients following noncardiac surgery [OR: 2.17, 95% CI: 1.82–2.59, $P < 0.001$; test for subgroup difference, $P = 0.02$; Figure 5].

Sensitivity analysis and publication bias

Sensitivity analysis by removing a single study at a time did not significantly change the outcomes, indicating the robustness of our results. A significant asymmetry on the funnel plot [Figure 7] and the Egger's test result indicated potential publication bias ($P = 0.002$). For adjusting the publication bias, we used the trim-and-fill analysis to impute potentially missing studies. After combining the hypothetical seven studies, the results were not substantially different (corrected OR = 2.15, 95% CI: 1.75–2.64, $P < 0.001$), which suggested that the outcome of our meta-analysis was reliable.

DISCUSSION

This meta-analysis was conducted to clarify the impact of preoperative frailty on PNDs in elderly patients

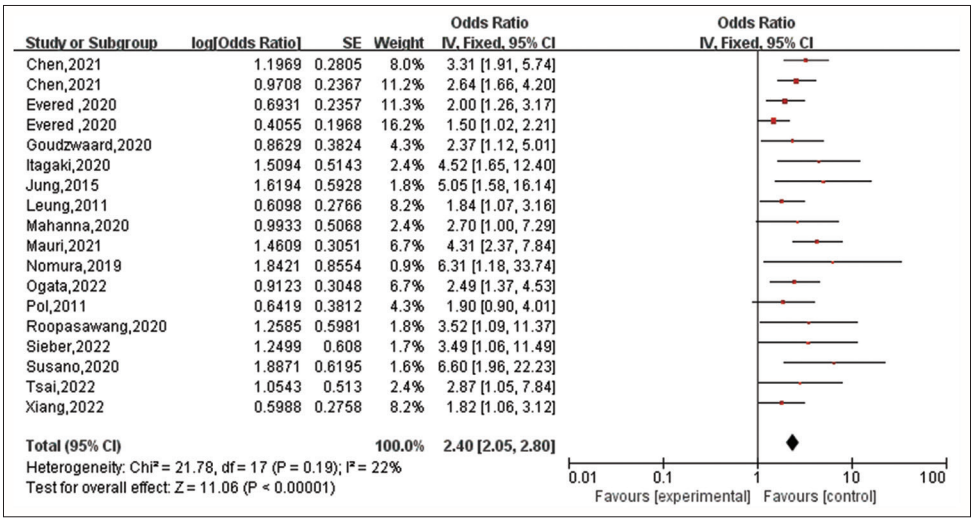

Figure 2: Forest plots for the association between frailty and perioperative neurocognitive disorders. PNDs = Perioperative neurocognitive disorders

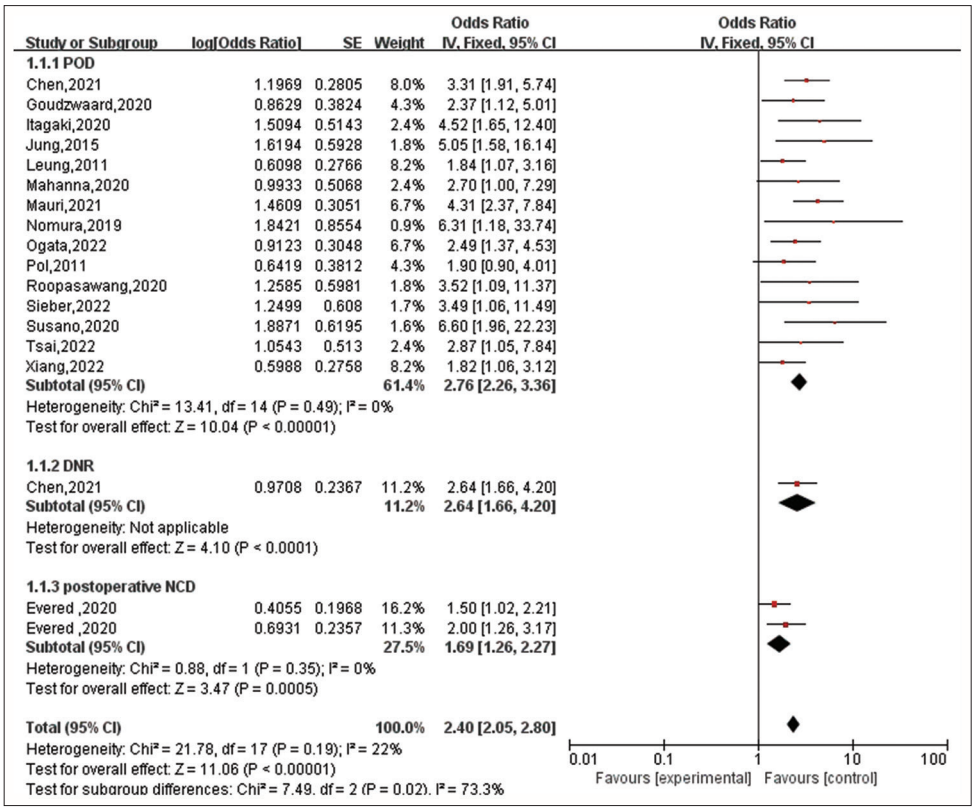

Figure 3: Forest plots for the association between frailty and the different subtypes of perioperative neurocognitive disorders. POD = Postoperative delirium, DNR = Delayed neurocognitive recovery, postoperative NCD = Postoperative neurocognitive disorder, PNDs = Perioperative neurocognitive disorders

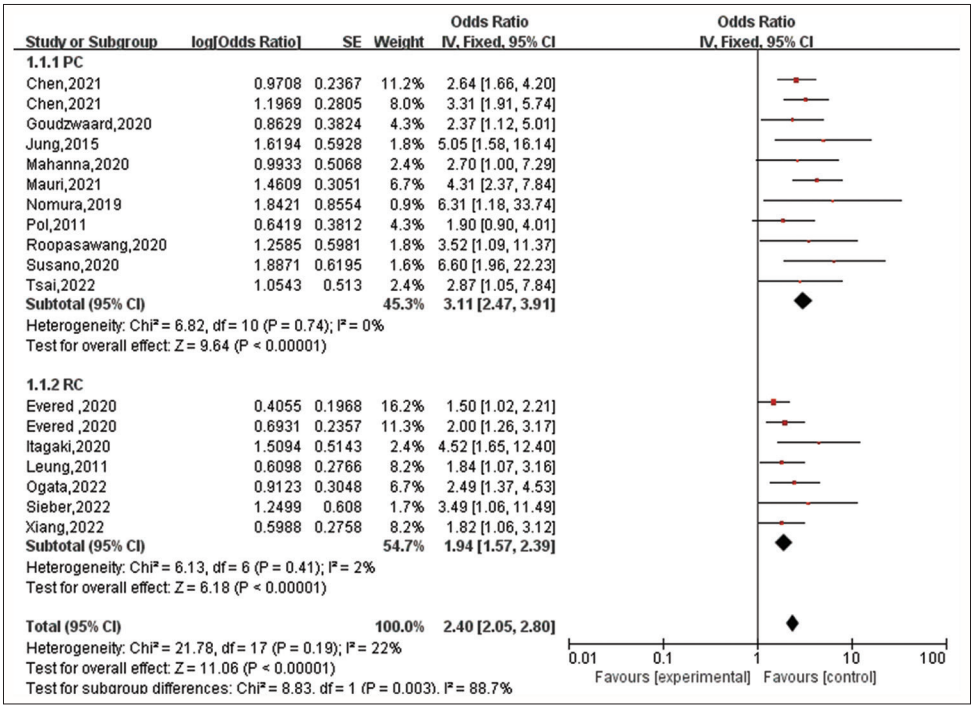

Figure 4: Forest plots for subgroup analyses of study design

undergoing elective surgery. Sixteen studies enrolling 4805 elderly patients were identified and our results showed an independent association between preoperative frailty and PNDs in older patients through combining the outcomes of updated studies, which indicated that it was of utmost importance for early assessment and intervention of frailty to prevent PNDs in geriatric surgical patients.

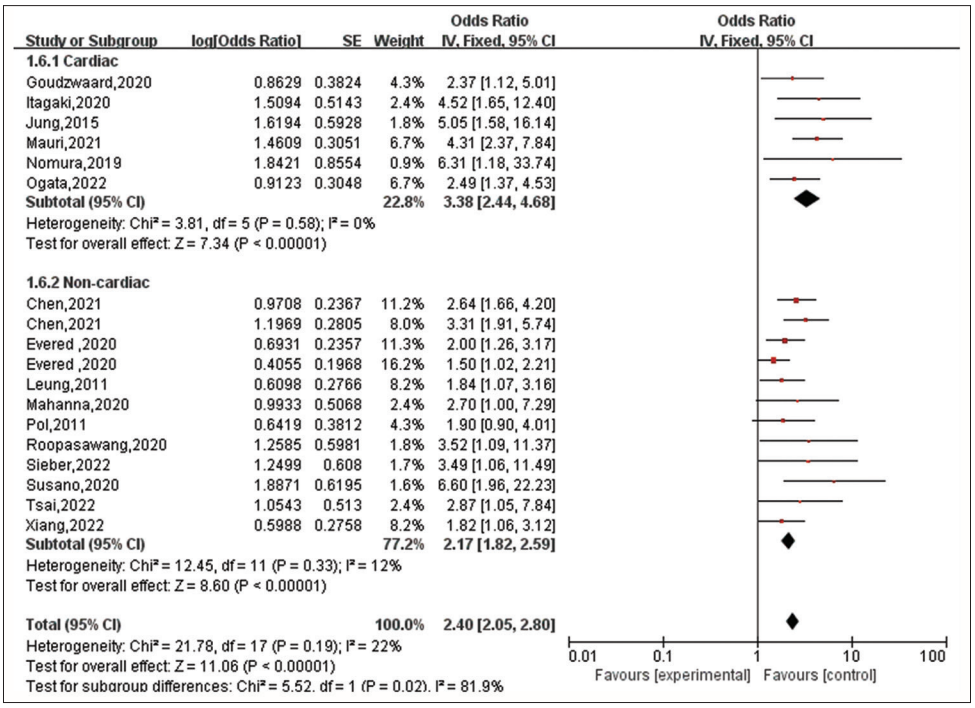

Figure 5: Forest plots for subgroup analyses of cardiac and noncardiac surgeries

According to the updated consensus, PNDs referred to neurocognitive abnormalities identified during the perioperative period, including POD, DNR, and postoperative NCD.[1] For elderly patients with more predisposing risk factors, PNDs were the most frequent complication after anesthesia and surgery.[2] POD was defined as an acute and fluctuating alteration in the mental state, which typically occurred within 7 days after surgery. DNR indicated a new-onset cognitive decline within 30 days of surgery, and postoperative NCD specifically referred to cognitive decline detected between 30 days and 1 year after surgery.[33] Patients with PNDs were exposed to the risk of prolonged length of hospital stay, cognitive dysfunction, and mortality.[4] Currently, the best management was the prevention of underlying risk factors due to no effective treatment for PNDs.[34]

Several risk factors were reported to be related with PNDs, including preoperative cognitive impairment, advanced age, inappropriate depth of anesthesia, and poor pain control.[1] Notably, preoperative frailty was regarded as a predisposing factor for PNDs.[18] Frailty was a multidimensional syndrome characterized by decreased physical reserve and resistance to stressors, which was associated with adverse clinical outcomes, such as hospitalization, depression, and mortality.[35] As a common geriatric syndrome, most old patients with frailty were accompanied by preoperative cognitive impairment, which intensified the risk for the occurrence of PNDs.[2,36] Furthermore, a prior research demonstrated that inflammatory mediators were overproduced in frail older individuals, which might result in an increased incidence of PNDs.[2,37] Our result was consistent with a recent review, showing that preoperative frailty was associated with an increase incidence of cognitive decline at 3 and 12 months postoperatively.[36] Another meta-analysis showed that preoperative frailty was an independent risk factor for POD;[38] by contrast, we investigated the long-term cognitive outcomes of elderly surgical patients with frailty.

Although the low heterogeneity was observed in the study, subgroup analyses were performed to detect potential sources of heterogeneity. The results did not affect the relationship between preoperative frailty and PNDs, which supported the robustness of our finding that preoperative frailty was highly correlated with PNDs. Interestingly, in the subgroup analysis based on study design, a more significant correlation was found in prospective cohort studies, which further proved the reliability of our result due to the few potential sources of bias in prospective studies.[39] In addition, the subgroup analysis showed a more remarkable association in elderly patients following cardiac surgery, which might attribute to the fact that frail patients were vulnerable to the substantial stress from cardiac surgery to develop PNDs.[40] Therefore, preoperative assessment and management of frailty are crucial to preventing PNDs, particularly in patients undergoing cardiac surgery.

Various frailty or PND assessment methods were applied in selected studies. Although multiple preoperative frailty measurement tools were developed, no gold standard assessment was determined in clinical practice. In this

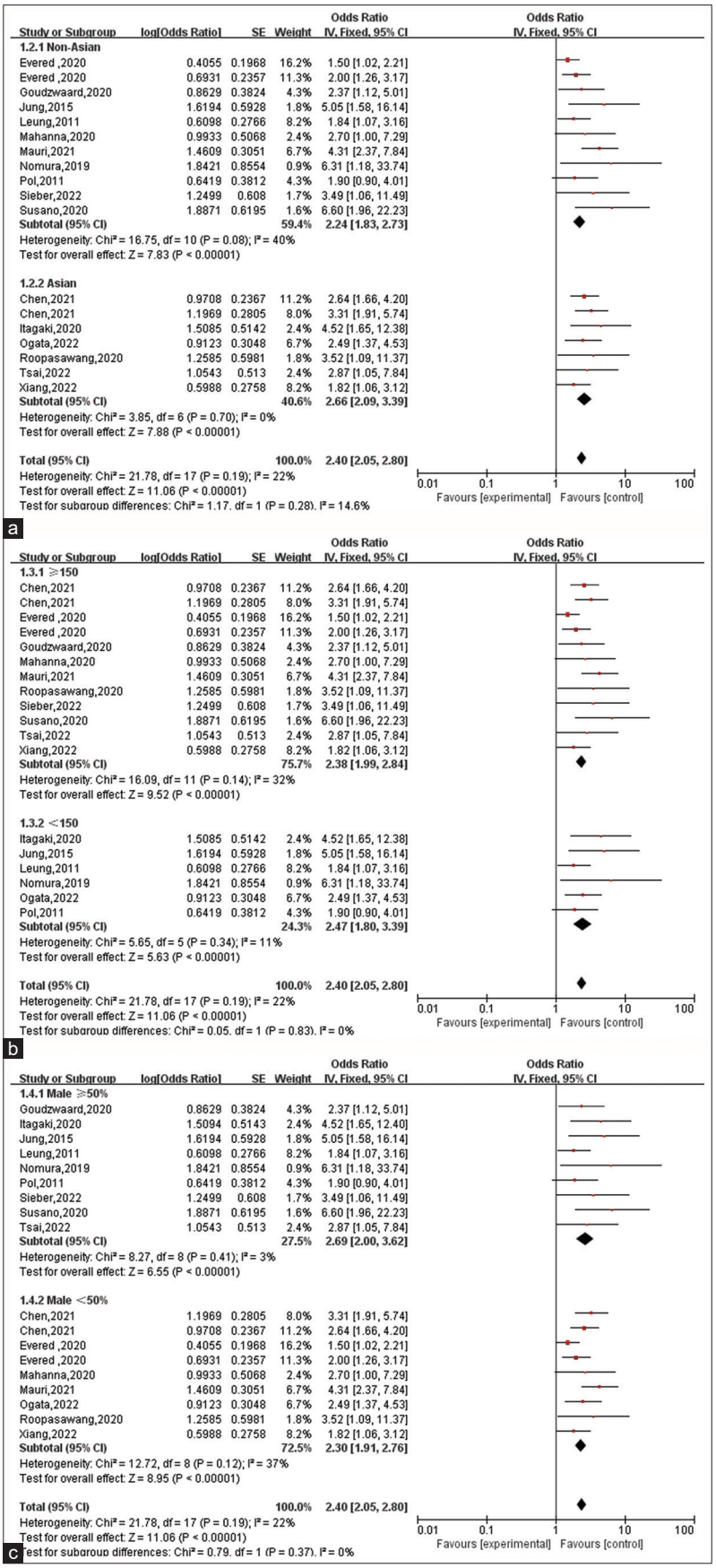

Figure 6: Contd...

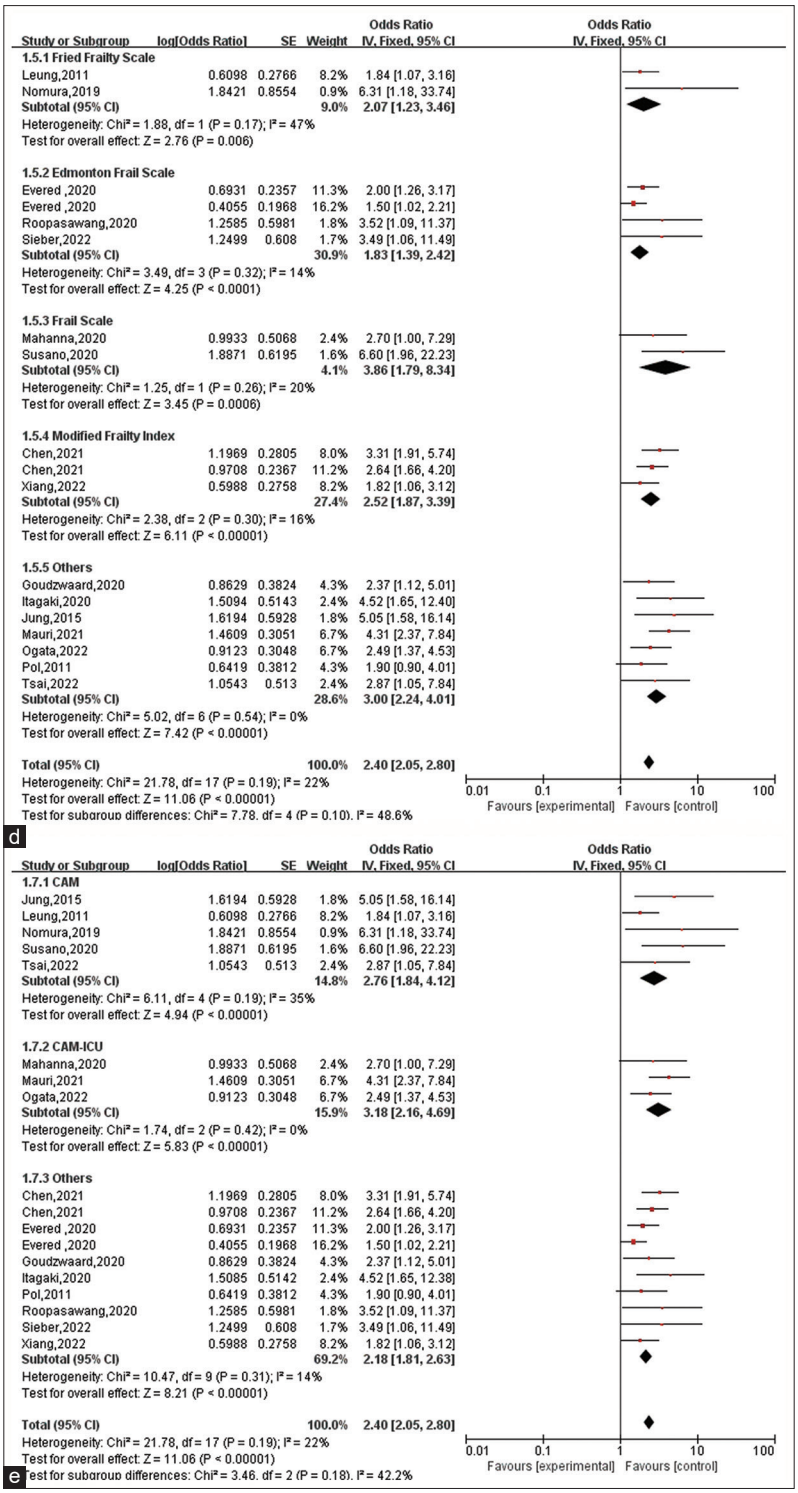

Figure 6: Forest plots for subgroup analysis. (a) study location; (b) sample size; (c) gender; (d) frailty measurement scales; (e) perioperative neurocognitive disorders diagnosis scales

meta-analysis, the FRAIL Scale, the Edmonton Frail Scale, the Modified Frailty index, and the Fried Frailty Scale were applied to assess frailty. Similarly, this meta-analysis covered a wide variety of PND diagnosis tools including CAM, CAM-ICU, ICDSC, and DSM-V. Our results showed that no matter which frailty or PNDs assessment tools were applied, there remained a strong relationship between preoperative frailty and PNDs. Future research should reach a consensus to define the most appropriate assessment tool of frailty, which could increase the implementation of preoperative frailty assessment in routine clinical settings and optimize patient management.

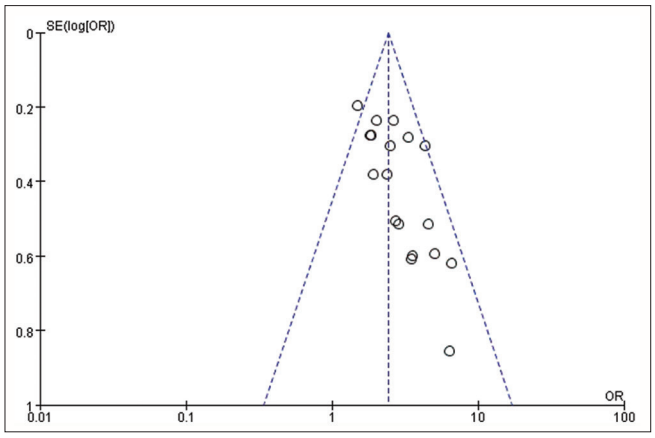

Figure 7: Funnel plot for the publication bias underlying the association between frailty and perioperative neurocognitive disorders

Given the adverse influence of PNDs, researchers focused on the management of PNDs to decrease the occurrence and improve postoperative outcomes. Based on the findings of our meta-analysis, we considered that preoperative prompt identification and intervention of frailty might reduce the incidence of PNDs. However, a randomized controlled trial showed that a geriatric liaison intervention for frailty was ineffective for PNDs in frail elderly patients with cancer; nevertheless, the result might be affected by the small sample size.[41] Indeed, several medical societies recommended that frailty should be assessed before surgery in older adults to reduce the incidence of postoperative complications.[42,43] In addition, a recent review suggested that multimodal prehabilitation based on frailty syndrome might be effective in improving postoperative outcomes.[44] Therefore, sufficient powerful trials are still needed to determine the efficacy of preoperative frailty intervention on the occurrence of PNDs.

The strengths of this review were as follows. First, this was the first meta-analysis to evaluate the correlation between preoperative frailty and PNDs in elderly surgical patients, which explored long-term cognitive outcomes of elderly surgical patients with frailty. In addition, only studies with multivariate analysis data were included, which minimized the potential impact of confounding factors on the result. Moreover, the number of included studies was larger in our meta-analysis, which improved the reliability of our results.

Our meta-analysis also exhibited several limitations. First, the amount of data available for DNR and postoperative NCD was limited, leading to a low level of evidence. Second, the potential confounding factors leading to clinical heterogeneity could not be excluded, such as various assessment tools of frailty and PNDs as well as different follow-up duration. Finally, the scope of our analysis was restricted by the advanced age, which could not provide a broader correlation between preoperative frailty and PNDs. Thus, future high-quality researches were needed to further clarify the relationship of preoperative frailty and PNDs.

CONCLUSION

This meta-analysis suggested that preoperative frailty might be associated with a higher risk of PNDs in geriatric patients who underwent elective surgery. Therefore, early identification and intervention of frailty before anesthesia and surgery was crucial to decrease the incidence of PNDs and enhance prognosis.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Full search strategy

Database	Keywords
1	("Frail Elderly"[Mesh]) OR "Frailty"[Mesh]
2	(frail[Title/Abstract]) OR (frailty[Title/Abstract])
3	1OR2
4	(("Cognitive Dysfunction"[Mesh]) OR "Delirium"[Mesh]) OR "Neurocognitive Disorders"[Mesh]
5	((((((((((neurocognitive impairment[Title/Abstract]) OR (cognitive impairment[Title/Abstract])) OR (cognitive decline[Title/Abstract])) OR (neurological complications[Title/Abstract])) OR (cognitive complications[Title/Abstract])) OR (dementia[Title/Abstract])) OR (delirious[Title/Abstract])) OR (acute confusional syndrome[Title/Abstract])) OR (acute confusional[Title/Abstract])) OR (POD[Title/Abstract])) OR (POCD[Title/Abstract])) OR (deliri*[Title/Abstract])
6	4OR5
7	(((((((((postoperative[Title/Abstract]) OR (operation*[Title/Abstract])) OR (surgery[Title/Abstract])) OR (anaesthesia[Title/Abstract])) OR (anesthesia[Title/Abstract])) OR (perioperati*[Title/Abstract])) OR (postoperati*[Title/Abstract])) OR (surg*[Title/Abstract])) OR (operati*[Title/Abstract])
8	(((("Prospective Studies"[Mesh]) OR "Retrospective Studies"[Mesh]) OR "Cohort Studies"[Mesh]) OR "Observational Study" [Publication Type]
9	(((retrospective*[Title/Abstract]) OR (prospective*[Title/Abstract])) OR (cohort stud*[Title/Abstract])) OR (observational*[Title/Abstract])
10	8OR9
11	3AND6AND7AND10
Pubmed	348
1	frail: ab, ti OR frailty: ab, ti
2	'frailty'/exp OR 'frail elderly'/exp
3	1OR2
4	'cognitive defect'/exp OR 'delirium'/exp OR 'disorders of higher cerebral function'/exp
5	'neurocognitive impairment':ab, ti OR 'cognitive impairment':ab, ti OR 'cognitive decline':ab, ti OR 'neurological complications':ab, ti OR 'cognitive complications':ab, ti OR dementia: ab, ti OR delirious: ab, ti OR 'acute confusional syndrome':ab, ti OR 'acute confusional':ab, ti OR pod: ab, ti OR pocd: ab, ti OR deliri*:ab, ti
6	4OR5
7	postoperative: ab, ti OR operation*:ab, ti OR surgery: ab, ti OR anaesthesia: ab, ti OR anesthesia: ab, ti OR perioperati*:ab, ti OR postoperati*:ab, ti OR surg*:ab, ti OR operati*:ab, ti
8	'prospective study'/exp OR 'retrospective study'/exp OR 'cohort analysis'/exp OR 'observational study'/exp
9	retrospective*:ab, ti OR prospective*:ab, ti OR 'cohort stud*':ab, ti OR observational*:ab, ti
10	8OR9
11	3AND6AND7AND10
Embase	720
1	((((TS=(frail elderly))) OR TS=(frailty))) OR TS=(frail)
2	((((((((((((((TS=(Cognitive Dysfunction)) OR TS=(Delirium)) OR TS=(Neurocognitive Disorders)) OR TS=(neurocognitive impairment)) OR TS=(cognitive impairment)) OR TS=(cognitive decline)) OR TS=(neurological complications)) OR TS=(cognitive complications)) OR TS=(dementia)) OR TS=(delirious)) OR TS=(acute confusional syndrome)) OR TS=(acute confusional)) OR TS=(POD)) OR TS=(POCD)) OR TS=(deliri*)
3	(((((((((TS=(postoperative)) OR TS=(operation*)) OR TS=(surgery)) OR TS=(anaesthesia)) OR TS=(anesthesia)) OR TS=(perioperati*)) OR TS=(postoperati*)) OR TS=(surg*)) OR TS=(operati*)
4	(((TS=(prospective*)) OR TS=(retrospective*)) OR TS=(cohort stud*)) OR TS=(observational*)
5	1AND2AND3AND4
Web of Science	660

Supplementary Table 2: PRISMA 2020 Checklist

Section and topic	Item number	Checklist item	Location where item is reported
		Title	
Title	1	Identify the report as a systematic review	Page 1
		Abstract	
Abstract	2	See the PRISMA 2020 for Abstracts checklist	Page 1
		Introduction	
Rationale	3	Describe the rationale for the review in the context of existing knowledge	Page 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses	Page 2-3
		Methods	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	Page 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	Page 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary Table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process	Page 4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process	Page 4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect	Page 4
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	Page 4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process	Page 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results	Page 5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5))	Table 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses	Page 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used	Page 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression)	Page 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results	Page 5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	Page 5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	NA
		Results	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	Page 5-6

Contd...

Supplementary Table 2: Contd...

Section and topic	Item number	Checklist item	Location where item is reported
		Results	
Study characteristics	17	Cite each included study and present its characteristics	Page 6-7
Risk of bias in studies	18	Present assessments of risk of bias for each included study	Page 8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots	Page 7
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 6-7
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	Page 7
	20c	Present results of all investigations of possible causes of heterogeneity among study results	Page 7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results	Page 8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	Page 8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	NA
		Discussion	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence	Page 8
	23b	Discuss any limitations of the evidence included in the review	Page 11
	23c	Discuss any limitations of the review processes used	Page 11
	23d	Discuss implications of the results for practice, policy, and future research	Page 9-10
		Other information	
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered	Page 3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol	NA
Support	25	Describe sources of financial or nonfinancial support for the review, and the role of the funders or sponsors in the review	Page 11
Competing interests	26	Declare any competing interests of review authors	Page 11
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review	NA

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71. NA: Not available