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

#### Shan Zhao<sup>1,2</sup>, Bei Wang<sup>3</sup>, Meinv Liu<sup>1</sup>, Dongdong Yu<sup>1</sup>, Jianli Li<sup>1</sup>

<sup>1</sup>Department of Anesthesiology, Hebei General Hospital, Shijiazhuang, Hebei, China, <sup>2</sup>Graduate Faculty, North China University of Science and Technology, Tangshan, Hebei, China, <sup>3</sup>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, P = 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) 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

How to cite this article: Zhao S, Wang B, Liu M, Yu D, Li J. The impact of preoperative frailty on perioperative neurocognitive disorders in elderly patients: A systematic review and meta-analysis. J Res Med Sci 2024;29:47.

## 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).<sup>[1]</sup> The incidence of PNDs ranged from 9% to 41% in general population, while it occurred up to 65% in older individuals.<sup>[2,3]</sup> 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

Access	this article online
Quick Response Code:	Website: https://journals.lww.com/jrms DOI: 10.4103/jrms.jrms_694_23

medical costs and decreased quality of patient's life.<sup>[4,5]</sup> Unfortunately, the mechanisms underlying the pathogenesis of PNDs remained elusive, which hindered the effective treatment for cognitive disorders.<sup>[2]</sup> 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.<sup>[6-8]</sup> Frailty as a common geriatric syndrome was considered a predisposing factor for POD in the European Society of Anesthesiology Guidelines.<sup>[9]</sup> Frailty was a clinical state of decreased physical reserve

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow\_reprints@wolterskluwer.com

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

Submitted: 17-Oct-2023; Revised: 05-May-2024; Accepted: 25-May-2024; Published: 30-Jul-2024

REVIEW ARTICLE

and increased vulnerability to stressors due to accumulative declines of multiple physiological functions.<sup>[10]</sup> The incidence of frailty reportedly claimed to range from 25% to 40% in older patients undergoing major surgery.<sup>[11]</sup> Frailty conferred a higher risk of negative postoperative outcomes such as fall, hospitalization, disability, and death.<sup>[12]</sup> Besides, several studies demonstrated that preoperative frailty might be related to an increase of PNDs.<sup>[13,14]</sup> 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.<sup>[15]</sup> 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;<sup>[16]</sup> (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<sup>2</sup> 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<sup>[14,18-22]</sup> and 10 were non-Asian.<sup>[23-32]</sup> Among these studies, 6 studies were retrospective,[19,20,22,24,28,32] while the other 10 studies were prospective.<sup>[14,18,21,23,25-27,29-31]</sup> Six studies included patients undergoing cardiac surgeries, [20,22,26,27,30,31] and the other 10 studies included patients following noncardiac surgeries.<sup>[14,18,19,21,23-25,28,29,32]</sup> 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

	D
	nwc
	0
	ade
	d
	frc
D,	Ĕ
õ	htt
p/I	0.1
ō	jo
Ĩ	urr
2	ล
Ξ	s./
ğ	≷
g	
Ry	m
Ξ	/jrr
2	SUL
Ē	by
6	Ψ
f3	Ð
õ	S₩
6	ĕ
Ă	Ĭ
]d/	a
B	12
a8	m
ŝ	ŭ
+	n1:
a6	Q
R	Z4
5	a +
Ē	2
	F
ň	N
/80	gb
03	°≓
20	04
)24	X
	ΛiO
	Ю
	Ň
	Õ
	(1)
	ž

Table 1: Ché	aracteristic	s of th	e inclu	ded st	udies								
Study (year) 1	-ocation	Study	Sample	Mean	Male, T	ype of	Frailty	Frailty	PNDs	PNDs (n)	Follow-up	AOR (95%CI)	Adjusted variables
		design	size	age	n (%) s	urgery	measurement	( <u>'</u>	measurement		duration		
Leung <i>et al.</i> [2011) <sup>[24]</sup>	The US	RC	63	72.3	34 (53.97) G al sl th	ieneral, rthroplasty, pine, horacic	Fried Frailty Scale	21	CAM	POD 16	2 days after surgery	1.84 (1.07-3.15)	Age, ADL dependence, IADL dependence, ITCS score, GDS score and preoperative depression score
Pol <i>et al.</i> ī (2011) <sup>[25]</sup> ŀ	The Vetherlands	PC	142	68.0	100 (70.42) V sı	'ascular urgery	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 <i>et al.</i> ( (2015) <sup>[26]</sup>	Canada	PC	133	71.0	98 (73.68) C sı	ardiac urgery	Modified fried criteria	72	CAM	POD 24	Until discharge	5.05 (1.58-16.13)	EuroSCORE II
Nomura <i>et al.</i> 7 (2019) <sup>[27]</sup>	The US	РС	133	72.0	97 (72.93) C si	ardiac urgery	Fried Frailty Scale	44	CAM	POD 56	Until discharge	6.31 (1.18–33.74)	Age, sex, education and EuroSCORE
Goudzwaard <i>et al.</i> (2020) <sup>[30]</sup>	The Netherlands	PC	543	79.1	297 (54.7) Tr	AVI	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
ltagaki <i>et al.</i> ] (2020) <sup>[22]</sup>	lapan	RC	89	74.9	57 (64.04) C sı	ardiac urgery	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 <sup>-</sup> <i>et al.</i> (2020) <sup>[29]</sup>	The US	PC	167	71.0	75 (44.91) N si	loncardiac urgery	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 <sup>]</sup> <i>et al.</i> (2020) <sup>[21]</sup>	Thailand	PC	200	72.0	44 (22) O sı	)rthopedic urgery	Edmonton Frail Scale	46	4AT-Test	POD 25	Until discharge	3.52 (1.09–12.26)	Age, sex, type of surgery and comorbidities
Susano <i>et al.</i> <sup>-</sup> (2020) <sup>[23]</sup>	The US	PC	219	75.0	124 (56.62) S si	urgery	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 <i>et al. 1</i> (2020) <sup>[28]</sup>	Aulstralia	RC	300	70.1	103 (34.33) H re	lip joint eplacement	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 IO, smoking, hypertension, history of acute myocardial infarction and diabetes
Chen <i>et al.</i> ( (2021) <sup>[14]</sup>	China	PC	383	72.7	132 (34.46) To 0	otal joint rthroplasty	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

## Zhao, et al.: Preoperative frailty affects postoperative cognition

| 2024 |

Contd...

Downloaded from http://journals.lww.com/jrms by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AW nYQp/IIQrHD3i3D00dRyi7TvSFI4Cf3VC4/OAVpDDa8K2+Ya6H515kE= on 08/03/2024

Table 1: Coi	ntd												
Study (year)	Location	Study	Sample	Mean	Male,	Type of	Frailty	Frailty	PNDs	PNDs ( <i>n</i> )	Follow-up	AOR (95%CI)	Adjusted variables
		design	Size	age	(%) U	surgery			measurement				
Mauri <i>et al.</i>	The US	PC	661	82.3	322 (48.71	) TAVR	Essential frailty	199	CAM-ICU	POD 66	7 days after	4.31 (2.37-7.87)	Sex, atrial fibrillation,
(2021) <sup>[31]</sup>							toolset				surgery		pneumonia, stroke, vascular complication and general anesthesia
Ogata <i>et al.</i> . (2022) <sup>[20]</sup>	lapan	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 <i>et al.</i> (2022) <sup>[32]</sup>	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 <i>et al.</i> (2022) <sup>[18]</sup>	Taiwan	РС	345	AN	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 <i>et al.</i> (2022) <sup>[19]</sup>	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=Retrospectiv model for intensiv attention, abbrevi MMSE=Mini-meni index; IQ=Intellige delirium; AOR=Ad	e cohort; PC= e care unit; D5 ated mental to al state exam nce quotient; justed odds ra	Prospective SM-IV=Diagr sst - 4, acuté ination; CRF SII=Systemic atio; CI=Con	cohort; NA nostic and s e change; F >=C-reactiv c immuneir fidence int	\=Not ava statistical ?CI=Relis ve protein iflammatik erval	ilable; TAVI=T manual of mer able change in c; ASA=Americ on index; NYH.	ranscatheter aort tial disorders, fou dex; IADL=Instru dex; IADL=Instru an Society of Ane a=New York Hear	ic valve implantation; th edition; DSM- V=D mental activities of d sethesiologists; CCI= tAssociation; GFR=C	TAVR=T SSM, fifth aily living Charlson Slomerula	ranscatheter aortic va edition; DOS=Deliriun g; ADL=Activities of ds I Comorbidity Index; E ar filtration rate; AFR=A	Ive replaceme 1 observation ally living; TIC uroSCORE II: ulbumin-fibrinc	ant; CAM=Confusic score; ICDSC=Inte S=Telephone inter =European System gen ratio; PNDs=P	on assessment method ansive care delirium scr view for cognitive; GD: view for Cardiac Operative erioperative neurocogr	, CAM-ICU=Confusion assessment sening checklist; 4AT-Test=Arousal, S=The Geriatric Depression Scale; Risk Evaluation II; BMI=Body mass itive disorders; POD=Postoperative

Zhao, et al.: Preoperative frailty affects postoperative cognition

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

Table 2: Quality assessment based on Newcastle-Ottawa Scale

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

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; P = 0%; Figure 3].

#### **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

				Odds Ratio	Odds	Ratio	
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixe	d, 95% Cl	
Chen,2021	1.1969	0.2805	8.0%	3.31 [1.91, 5.74]			
Chen,2021	0.9708	0.2367	11.2%	2.64 [1.66, 4.20]			
Evered ,2020	0.6931	0.2357	11.3%	2.00 [1.26, 3.17]			
Evered ,2020	0.4055	0.1968	16.2%	1.50 [1.02, 2.21]			
Goudzwaard,2020	0.8629	0.3824	4.3%	2.37 [1.12, 5.01]		<b> </b> →→	
Itagaki,2020	1.5094	0.5143	2.4%	4.52 [1.65, 12.40]			
Jung,2015	1.6194	0.5928	1.8%	5.05 [1.58, 16.14]			
Leung,2011	0.6098	0.2766	8.2%	1.84 [1.07, 3.16]			
Mahanna,2020	0.9933	0.5068	2.4%	2.70 [1.00, 7.29]		<u> </u>	
Mauri,2021	1.4609	0.3051	6.7%	4.31 [2.37, 7.84]			
Nomura,2019	1.8421	0.8554	0.9%	6.31 [1.18, 33.74]			-
Ogata,2022	0.9123	0.3048	6.7%	2.49 [1.37, 4.53]			
Pol,2011	0.6419	0.3812	4.3%	1.90 [0.90, 4.01]			
Roopasawang,2020	1.2585	0.5981	1.8%	3.52 [1.09, 11.37]		· · · · ·	
Sieber,2022	1.2499	0.608	1.7%	3.49 [1.06, 11.49]		· · ·	
Susano,2020	1.8871	0.6195	1.6%	6.60 [1.96, 22.23]			
Tsai,2022	1.0543	0.513	2.4%	2.87 [1.05, 7.84]		· · · · ·	
Xiang,2022	0.5988	0.2758	8.2%	1.82 [1.06, 3.12]			
Total (95% CI)			100.0%	2.40 [2.05, 2.80]		•	
Heterogeneity: Chi <sup>2</sup> = 2	1.78, df = 17 (P = 0	0.19); I <sup>2</sup> =	22%		0.01 0.1	1 10	100
Test for overall effect: Z	= 11.06 (P < 0.00)	001)			Favours (experimental)	Favours (control)	.00

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

				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.1.1 POD					
Chen,2021	1.1969	0.2805	8.0%	3.31 [1.91, 5.74]	
Goudzwaard,2020	0.8629	0.3824	4.3%	2.37 [1.12, 5.01]	
Itagaki,2020	1.5094	0.5143	2.4%	4.52 [1.65, 12.40]	
Jung,2015	1.6194	0.5928	1.8%	5.05 [1.58, 16.14]	
Leung,2011	0.6098	0.2766	8.2%	1.84 [1.07, 3.16]	
Mahanna,2020	0.9933	0.5068	2.4%	2.70 [1.00, 7.29]	
Mauri,2021	1.4609	0.3051	6.7%	4.31 [2.37, 7.84]	
Nomura,2019	1.8421	0.8554	0.9%	6.31 [1.18, 33.74]	
Ogata,2022	0.9123	0.3048	6.7%	2.49 [1.37, 4.53]	
Pol,2011	0.6419	0.3812	4.3%	1.90 [0.90, 4.01]	
Roopasawang,2020	1.2585	0.5981	1.8%	3.52 [1.09, 11.37]	
Sieber,2022	1.2499	0.608	1.7%	3.49 [1.06, 11.49]	
Susano,2020	1.8871	0.6195	1.6%	6.60 [1.96, 22.23]	
Tsai,2022	1.0543	0.513	2.4%	2.87 [1.05, 7.84]	
Xiang,2022	0.5988	0.2758	8.2%	1.82 [1.06, 3.12]	
Subtotal (95% CI)			61.4%	2.76 [2.26, 3.36]	•
Heterogeneity: Chi <sup>2</sup> = 1	3.41, df = 14 (P = 0	0.49); I <sup>2</sup> =	0%		
Test for overall effect: Z	= 10.04 (P < 0.00)	001)			
	•				
1.1.2 DNR					
Chen.2021	0.9708	0.2367	11.2%	2.64 [1.66, 4.20]	
Subtotal (95% CI)			11.2%	2.64 [1.66, 4.20]	•
Heterogeneity: Not app	licable				
Test for overall effect: Z	= 4.10 (P < 0.000	1)			
		· ·			
1.1.3 postoperative NC	D				
Evered .2020	0.4055	0.1968	16.2%	1.50 [1.02, 2.21]	
Evered 2020	0.6931	0.2357	11.3%	2.00 [1.26, 3.17]	
Subtotal (95% CI)			27.5%	1.69 [1.26, 2.27]	•
Heterogeneity: Chi <sup>2</sup> = 0	.88. df = 1 (P = 0.3	5): $I^2 = 0.9$	8		
Test for overall effect: Z	= 3.47 (P = 0.000)	5)			
		·			
Total (95% CI)			100.0%	2.40 [2.05, 2.80]	•
Heterogeneity: Chi <sup>2</sup> = 2	1.78, df = 17 (P = 0	).19); I <sup>2</sup> =	22%		
Test for overall effect: Z	= 11.06 (P < 0.00)	001)			U.U1 U.1 1 10 100
Test for subaroup differ	rences: Chi <sup>2</sup> = 7.49	3. df = 2 (	P = 0.02).	I <sup>2</sup> = 73.3%	Favours (experimental) Favours (control)

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

				Oddo Potio	Oddo Potio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV. Fixed, 95% CI	IV. Fixed, 95% Cl
1.1.1 PC	iog outor tuttor	02		In the second se	
Chen.2021	0.9708	0.2367	11.2%	2.64 [1.66, 4.20]	
Chen.2021	1,1969	0.2805	8.0%	3.31 [1.91, 5.74]	
Goudzwaard.2020	0.8629	0.3824	4.3%	2.37 [1.12, 5.01]	
Juna,2015	1.6194	0.5928	1.8%	5.05 [1.58, 16.14]	
Mahanna,2020	0.9933	0.5068	2.4%	2.70 [1.00, 7.29]	
Mauri,2021	1.4609	0.3051	6.7%	4.31 [2.37, 7.84]	
Nomura,2019	1.8421	0.8554	0.9%	6.31 [1.18, 33.74]	
Pol.2011	0.6419	0.3812	4.3%	1.90 [0.90, 4.01]	
Roopasawang,2020	1.2585	0.5981	1.8%	3.52 [1.09, 11.37]	
Susano,2020	1.8871	0.6195	1.6%	6.60 [1.96, 22.23]	
Tsai,2022	1.0543	0.513	2.4%	2.87 [1.05, 7.84]	
Subtotal (95% CI)			45.3%	3.11 [2.47, 3.91]	◆
Heterogeneity: Chi <sup>2</sup> = 6	.82, df = 10 (P = 0.3	74); l² = 0	)%		
Test for overall effect: Z	. = 9.64 (P < 0.0000	11)			
1.1.2 RC					
Evered .2020	0.4055	0.1968	16.2%	1.50 [1.02, 2.21]	
Evered .2020	0.6931	0.2357	11.3%	2.00 [1.26, 3.17]	
Itagaki,2020	1,5094	0.5143	2.4%	4.52 [1.65, 12,40]	
Leung,2011	0.6098	0.2766	8.2%	1.84 [1.07, 3.16]	
Ogata,2022	0.9123	0.3048	6.7%	2.49 [1.37, 4.53]	
Sieber,2022	1.2499	0.608	1.7%	3.49 [1.06, 11.49]	
Xiang,2022	0.5988	0.2758	8.2%	1.82 [1.06, 3.12]	
Subtotal (95% CI)			54.7%	1.94 [1.57, 2.39]	•
Heterogeneity: Chi <sup>2</sup> = 6	.13, df = 6 (P = 0.41	1); I <sup>2</sup> = 29	Хо		
Test for overall effect: 2	= 6.18 (P < 0.0000	11)			
Total (95% CI)			100.0%	2.40 [2.05, 2.80]	•
Heterogeneity: Chi <sup>2</sup> = 2	1 78 df = 17 (P = 0	19)  2=	22%		
Test for overall effect: 7	= 11 06 (P < 0 000	01)			0.01 0.1 1 10 100
reaction overall effect. 2					Francisco francisco e statu Francisco francisco N

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.

				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.6.1 Cardiac					
Goudzwaard, 2020	0.8629	0.3824	4.3%	2.37 [1.12, 5.01]	
Itagaki,2020	1.5094	0.5143	2.4%	4.52 [1.65, 12.40]	
Jung,2015	1.6194	0.5928	1.8%	5.05 [1.58, 16.14]	
Mauri,2021	1.4609	0.3051	6.7%	4.31 [2.37, 7.84]	
Nomura,2019	1.8421	0.8554	0.9%	6.31 [1.18, 33.74]	
Ogata,2022	0.9123	0.3048	6.7%	2.49 [1.37, 4.53]	
Subtotal (95% CI)			22.8%	3.38 [2.44, 4.68]	•
Heterogeneity: Chi <sup>2</sup> = 3	3.81, df = 5 (P = 0.5	8); I <sup>2</sup> = 09	%		
Test for overall effect: 2	Z = 7.34 (P < 0.000	D1)			
1.6.2 Non-cardiac					
Chen,2021	0.9708	0.2367	11.2%	2.64 [1.66, 4.20]	
Chen,2021	1.1969	0.2805	8.0%	3.31 [1.91, 5.74]	
Evered ,2020	0.6931	0.2357	11.3%	2.00 [1.26, 3.17]	
Evered ,2020	0.4055	0.1968	16.2%	1.50 [1.02, 2.21]	
Leung,2011	0.6098	0.2766	8.2%	1.84 [1.07, 3.16]	
Mahanna,2020	0.9933	0.5068	2.4%	2.70 [1.00, 7.29]	
Pol,2011	0.6419	0.3812	4.3%	1.90 [0.90, 4.01]	<b>+</b>
Roopasawang,2020	1.2585	0.5981	1.8%	3.52 [1.09, 11.37]	
Sieber,2022	1.2499	0.608	1.7%	3.49 [1.06, 11.49]	
Susano,2020	1.8871	0.6195	1.6%	6.60 [1.96, 22.23]	
Tsai,2022	1.0543	0.513	2.4%	2.87 [1.05, 7.84]	
Xiang,2022	0.5988	0.2758	8.2%	1.82 [1.06, 3.12]	
Subtotal (95% CI)			77.2%	2.17 [1.82, 2.59]	•
Heterogeneity: Chi <sup>2</sup> = 1	12.45, df = 11 (P = 0	).33); I <sup>z</sup> =	12%		
Test for overall effect: 2	Z = 8.60 (P < 0.000	D1)			
Total (95% CI)			100.0%	2.40 [2.05, 2.80]	•
Heterogeneity: Chi <sup>2</sup> = 2	21.78, df = 17 (P = 0	).19); I <sup>z</sup> =	22%		
Test for overall effect: 2	Z = 11.06 (P < 0.00)	001)			Eavoure [evperimental] Eavoure [control]
Test for subaroup diffe	erences: Chi² = 5.52	2. df = 1 (	P = 0.02).	l² = 81.9%	ravous (experimental) i avous (control)

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.<sup>[1]</sup> For elderly patients with more predisposing risk factors, PNDs were the most frequent complication after anesthesia and surgery.<sup>[2]</sup> 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.<sup>[33]</sup> Patients with PNDs were exposed to the risk of prolonged length of hospital stay, cognitive dysfunction, and mortality.<sup>[4]</sup> 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.<sup>[1]</sup> Notably, preoperative frailty was regarded as a predisposing factor for PNDs.<sup>[18]</sup> 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.<sup>[35]</sup> 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.<sup>[2,36]</sup> Furthermore, a prior research demonstrated that inflammatory mediators were overproduced in frail older individuals, which might result in an increased incidence of PNDs.<sup>[2,37]</sup> 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.<sup>[36]</sup> Another meta-analysis showed that preoperative frailty was an independent risk factor for POD;<sup>[38]</sup> 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.<sup>[39]</sup> 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.<sup>[40]</sup> 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

Zhao, et al.: Preoperative frailty affects postoperative cognition

					Odds Ratio	Odds Ratio
-	Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
	Evered .2020	0.4055	0.1968	16.2%	1.50 [1.02, 2.21]	
	Evered ,2020	0.6931	0.2357	11.3%	2.00 [1.26, 3.17]	
	Goudzwaard,2020	0.8629	0.3824	4.3%	2.37 [1.12, 5.01]	
	Jung,2015	1.6194	0.5928	1.8%	5.05 [1.58, 16.14]	
	Mahanna.2020	0.9933	0.5068	2.4%	2.70 [1.00, 7.29]	
	Mauri,2021	1.4609	0.3051	6.7%	4.31 [2.37, 7.84]	
	Nomura,2019	1.8421	0.8554	0.9%	6.31 [1.18, 33.74]	
	Pol,2011 Sigher 2022	0.6419	0.3812	4.3%	1.90 [0.90, 4.01]	
	Susano.2020	1.2435	0.6195	1.6%	6.60 [1.96, 22.23]	
	Subtotal (95% CI)			59.4%	2.24 [1.83, 2.73]	•
	Heterogeneity: Chi <sup>2</sup> = 1	6.75, df = 10 (P = 1	0.08); I <sup>2</sup> =	40%		
	lest for overall effect: 2	2 = 7.83 (P < 0.000	U1)			
	1.2.2 Asian					
	Chen,2021	0.9708	0.2367	11.2%	2.64 [1.66, 4.20]	
	Chen,2021	1.1969	0.2805	8.0%	3.31 [1.91, 5.74]	
	Itagaki,2020 Odata 2022	1.5085	0.5142	2.4%	4.52 [1.65, 12.38]	
	Roopasawang,2020	1.2585	0.5981	1.8%	3.52 [1.09, 11.37]	
	Tsai,2022	1.0543	0.513	2.4%	2.87 [1.05, 7.84]	
	Xiang,2022 Subtotal (95% CI)	0.5988	0.2758	8.2%	1.82 [1.06, 3.12]	
	Heterogeneity Chi <sup>2</sup> = 3	85 df = 6 (P = 0.7)	0): I <sup>2</sup> = 09	40.0%	2.00 [2.09, 5.59]	•
	Test for overall effect: 2	Z = 7.88 (P < 0.000	01)	•		
	Heterogonoity Ohiz	1 79 0 - 17 0	1 1 0 \- 12	100.0%	2.40 [2.05, 2.80]	▶ ▶ ▶ ▶ ▶ ▶ ▶ ▶ ▶ ▶ ▶ ▶ ▶ ▶ ▶ ▶ ▶ ▶ ▶
	Test for overall effect 7	Z = 11.06 (P < 0.00)	001)	2270		0.01 0.1 1 10 100
	Test for subaroup diffe	rences: Chi <sup>2</sup> = 1.1	7. df = 1 (	P = 0.28)	. I² = 14.6%	Favours [experimental] Favours [control]
2						
	-				Odds Ratio	Odds Ratio
-	Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
	1.3.1 ≈150 Chen 2021	0 0700	0.2367	11 2%	2.64 [1.66.4.20]	
	Chen,2021	1.1969	0.2805	8.0%	3.31 [1.91, 5.74]	
	Evered ,2020	0.4055	0.1968	16.2%	1.50 [1.02, 2.21]	
	Evered ,2020	0.6931	0.2357	11.3%	2.00 [1.26, 3.17]	
	Goudzwaard,2020 Mahanna 2020	0.8629	0.3824	4.3%	2.37 [1.12, 5.01]	
	Mauri.2021	1,4609	0.3051	6.7%	4.31 [2.37, 7.84]	
	Roopasawang,2020	1.2585	0.5981	1.8%	3.52 [1.09, 11.37]	
	Sieber,2022	1.2499	0.608	1.7%	3.49 [1.06, 11.49]	
	Susano,2020	1.8871	0.6195	1.6%	6.60 [1.96, 22.23]	
	Xiang.2022	0.5988	0.2758	8.2%	1.82 [1.06, 3.12]	
	Subtotal (95% CI)			75.7%	2.38 [1.99, 2.84]	•
	Heterogeneity: Chi <sup>2</sup> = 1	6.09, df = 11 (P = 0	0.14); I <sup>2</sup> =	32%		
	Test for overall effect: 2	Z = 9.52 (P < 0.000	01)			
	1.3.2 <150					
	Itagaki,2020	1.5085	0.5142	2.4%	4.52 [1.65, 12.38]	
	Jung,2015	1.6194	0.5928	1.8%	5.05 [1.58, 16.14]	
	Leung,2011 Nomura 2018	0.6098	0.2766	8.2%	1.84 [1.07, 3.16]	
	Ogata,2022	0.9123	0.3048	6.7%	2.49 [1.37, 4.53]	
	Pol,2011	0.6419	0.3812	4.3%	1.90 [0.90, 4.01]	+
	Subtotal (95% CI)		0.17 44	24.3%	2.47 [1.80, 3.39]	
	Test for overall effect 7	5.65, 01 = 5 (P = 0.3 7 = 5.63 (P < 0.000)	4); 1° = 1 1 01)	70		
	restion overall enect. 2		517			
	Total (95% CI)			100.0%	2.40 [2.05, 2.80]	
	Heterogeneity: Chi <sup>2</sup> = 2	21.78, df = 17 (P = 1	0.19); I <sup>2</sup> =	22%		0.01 0.1 1 10 100
	Test for subgroup diffe	rences: Chi <sup>2</sup> = 0.00	001) 5 df=1 (1	P = 0.83)	I <sup>2</sup> = 0%	Favours [experimental] Favours [control]
ŀ	Testion suburous unic	iences. on = 0.0.	5. ai – i a	- 0.037	1 - 0 %	
					Odds Ratio	Odds Ratio
-	Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
	1.4.1 Male ≥50%	0.0000	0 2024	4.000	2 27 14 42 5 643	
	Itagaki,2020	0.8629	0.5824	4.3%	2.37 [1.12, 5.01] 4.52 [1.65, 12.40]	
	Jung,2015	1.6194	0.5928	1.8%	5.05 [1.58, 16.14]	
	Leung,2011	0.6098	0.2766	8.2%	1.84 [1.07, 3.16]	
	Nomura,2019 Rol 2011	1.8421	0.8554	0.9%	6.31 [1.18, 33.74]	
	Sieber.2022	0.6419	0.3812	4.3%	1.90 [0.90, 4.01] 3.49 [1 06 11 40]	
	Susano,2020	1.8871	0.6195	1.6%	6.60 [1.96, 22.23]	
	Tsai,2022	1.0543	0.513	2.4%	2.87 [1.05, 7.84]	
	Subtotal (95% CI)	07	41.12 - 00	27.5%	2.69 [2.00, 3.62]	
	Heterogeneity: Chi* = 8	3.27, df = 8 (P = 0.4 7 = 6.55 /P ≤ 0.000	1); F= 39 01)	80		
	1.4.2 Male <50%					
	Chen,2021	1.1969	0.2805	8.0%	3.31 [1.91, 5.74]	
	Evered ,2020	0.9708	0.2307	16.2%	1.50 [1.02, 2.21]	
	Evered ,2020	0.6931	0.2357	11.3%	2.00 [1.26, 3.17]	
	Mahanna,2020	0.9933	0.5068	2.4%	2.70 [1.00, 7.29]	
	Mauri,2021	1.4609	0.3051	6.7%	4.31 [2.37, 7.84]	
	Ogata,2022 Roopasawang 2020	0.9123	0.3048	0.7%	2.49 [1.37, 4.53]	
	Xiang,2022	0.5988	0.2758	8.2%	1.82 [1.06, 3.12]	
	Subtotal (95% CI)			72.5%	2.30 [1.91, 2.76]	•
	Heterogeneity: Chi <sup>2</sup> = 1	2.72, df = 8 (P = 0.	12); I <sup>2</sup> = 3	87%		
	rest for overall effect: 2	L = 8.95 (P < 0.000)	U1)			
	Total (95% CI)			100.0%	2.40 [2.05, 2.80]	•
	Heterogeneity: Chi <sup>2</sup> = 2	21.78, df = 17 (P = 1	0.19); I² =	22%		
	Test for overall effect: 2	Z = 11.06 (P < 0.00)	001)	0-007	12-00	Favours [experimental] Favours [control]
10	🖬 escior subaroup diffe	rences: Chi* = 0.79	a, ui = 1 (l	r = 0.37)	1 = U%	

Figure 6: Contd...

Zhao, et al.: Preoperative frailty affects postoperative cognition

			Odds Ratio	Odds	Ratio
Study or Subgroup log[	Odds Ratio]	SE Weight	IV, Fixed, 95% CI	IV, Fixed	, 95% CI
1.5.1 Fried Frailty Scale	0.6000 0.0	200 0.00	4 04 14 07 0 4 61		
Nomura,2019	1.8421 0.85	554 0.9%	6.31 [1.18, 33.74]		
Subtotal (95% CI)		9.0%	2.07 [1.23, 3.46]		<b>•</b>
Heterogeneity: Chi <sup>2</sup> = 1.88, c	df = 1 (P = 0.17); I <sup>2</sup>	= 47%			
Test for overall effect: Z = 2.7	76 (P = 0.006)				
1.5.2 Edmonton Frail Scale					
Evered ,2020	0.6931 0.23	357 11.3%	2.00 [1.26, 3.17]		
Evered ,2020	0.4055 0.19	368 16.2%	1.50 [1.02, 2.21]		
Roopasawang,2020	1.2585 0.59	381 1.8%	3.52 [1.09, 11.37]		
Subtotal (95% CI)	1.2499 0.6	30.9%	1.83 [1.39, 2.42]		•
Heterogeneity: Chi <sup>2</sup> = 3.49, c	df = 3 (P = 0.32); I <sup>2</sup>	= 14%			
Test for overall effect: Z = 4.2	25 (P < 0.0001)				
153 Frail Scale					
Mahanna 2020	0.9933 0.50	168 24%	2 70 (1 00 7 29)		
Susano,2020	1.8871 0.61	195 1.6%	6.60 [1.96, 22.23]		
Subtotal (95% CI)		4.1%	3.86 [1.79, 8.34]		•
Heterogeneity: Chi <sup>2</sup> = 1.25, c	df = 1 (P = 0.26); I <sup>≥</sup>	= 20%			
lest for overall effect: Z = 3.4	45 (P = 0.0006)				
1.5.4 Modified Frailty Index					
Chen,2021	1.1969 0.28	805 8.0%	3.31 [1.91, 5.74]		<b>—</b>
Chen,2021	0.9708 0.23	367 11.2%	2.64 [1.66, 4.20]		
Xiang,2022 Subtotal (95% Ch	0.5988 0.23	158 8.2%	1.82 [1.06, 3.12]		٠
Heterogeneity: Chi <sup>2</sup> = 2.38 m	df = 2 (P = 0.30): P	= 16%	2.52 [1.67, 5.39]		•
Test for overall effect: Z = 6.1	11 (P < 0.00001)				
200329 NOX					
1.5.5 Others					
Goudzwaard,2020	0.8629 0.30	524 4.3% 142 2.4%	2.37 [1.12, 5.01]		
Jung 2015	1.6194 0.5	143 2.4%	5.05 [1.58, 16, 14]		
Mauri,2021	1.4609 0.30	051 6.7%	4.31 [2.37, 7.84]		
Ogata,2022	0.9123 0.30	048 6.7%	2.49 [1.37, 4.53]		<b>_</b> _
Pol,2011	0.6419 0.3	312 4.3%	1.90 [0.90, 4.01]	-	
Tsai,2022 Subtotal (05% CI)	1.0543 0.5	513 2.4%	2.87 [1.05, 7.84]		•
Heterogeneity: Chi <sup>2</sup> = 5.02 c	f = 6 (P = 0.54)	= 0%	5.00 [2.24, 4.01]		•
Test for overall effect: Z = 7.4	42 (P < 0.00001)				
T-A-L (OFN) CD		400.00	2 40 12 05 2 001		<b>A</b>
Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 21.78	df = 17 (P = 0.19)	100.0%	2.40 [2.05, 2.80]	·	•
Total (95% Cl) Heterogeneity: Chi² = 21.78, Test for overall effect: Z = 11	df = 17 (P = 0.19) .06 (P < 0.00001)	<b>100.0</b> % ; I <sup>z</sup> = 22%	2.40 [2.05, 2.80]	0.01 0.1 1	◆ 10 100
Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 21.78, Test for overall effect: Z = 11 Test for subaroup difference	, df = 17 (P = 0.19) .06 (P < 0.00001) es: Chi <sup>2</sup> = 7.78. df =	<b>100.0%</b> ; I <sup>2</sup> = 22% = 4 (P = 0.10)	2.40 [2.05, 2.80] 1 <sup>2</sup> = 48.6%	0.01 0.1 Favours (experimental)	♦ 10 100 Favours (control)
Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 21.78, Test for overall effect: Z = 11 Test for subaroup difference C	, df= 17 (P = 0.19) .06 (P < 0.00001) es: Chi² = 7.78. df=	<b>100.0%</b> ; I <sup>2</sup> = 22% = 4 (P = 0.10)	2.40 [2.05, 2.80]   <sup>2</sup> = 48.6% Odds Batio	0.01 0.1 favours (experimental)	10 100 Favours (control) Ratio
Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 21.78, Test for overall effect: Z = 11 Test for subarouo difference C Study or Subgroup logf	df= 17 (P = 0.19) .06 (P < 0.00001) s: Chi <sup>2</sup> = 7.78. df= (Odds Ratio]	100.0% ; I <sup>2</sup> = 22% = 4 (P = 0.10) <u>SE Weight</u>	2.40 [2.05, 2.80] .  ² = 48.6% Odds Ratio IV, Fixed, 95% CI	0.01 0.1 favours (experimental) Odds IV. Fixed	10 100 Favours [control] Ratio .95% CI
Total (95% Cl)         Helerogeneity: Chi <sup>™</sup> = 21.78,         Test for overall effect Z = 11         Test for subarouo difference         C         Study or Subgroup logf         1.7.1 CAM	df = 17 (P = 0.19) .06 (P < 0.00001) ss: Chi <sup>2</sup> = 7.78. df = (Odds Ratio]	100.0% ; I² = 22% = 4 (P = 0.10) <u>SE Weight</u>	2.40 [2.05, 2.80]   <sup>2</sup> = 48.6% Odds Ratio IV, Fixed, 95% CI	G.01 0.1 Favours (experimental) Odds IV, Fixed	10 100 Favours [control] Ratio .95% CI
Total (95% Cl) Heterogeneity: Chi <sup>™</sup> = 21.78, Test for overall effect Z = 11 Test for subaroup difference C Study or Subgroup log( 1.7.1 CAM Jung.2015	, df = 17 (P = 0.19) .06 (P < 0.00001) ss: Chi <sup>a</sup> = 7.78. df = <u>(Odds Ratio)</u> 1.6194 0.55	100.0% ; I <sup>2</sup> = 22% = 4 (P = 0.10) <u>SE Weight</u> 228 1.8%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio N. Fixed, 95% CI 5.05 [1.58, 16.14]	0.01 0.1 Favours (experimental) Odds IV, Fixed	10 100 Favours [control] Ratio .95% Cl
Total (95% CI) Heterogeneily: Chi¤ = 21.78, Test for overall effect. Z = 11 Test for subaroup difference C Study or Subgroup logf 1.7.1 CAM Jung,2015 Leung,2011 Normar 2019	, df = 17 (P = 0.19) .06 (P < 0.00001) sc: Chi <sup>2</sup> = 7.78. df = <u>(Odds Ratio)</u> 1.6194 0.52 0.6098 0.22 1.9410 0.92	100.0% ;   <sup>2</sup> = 22% = 4 (P = 0.10) <u>SE Weight</u> 328 1.8% 766 8.2%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio M. Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 5.31 (14.23, 74]	0.01 0.1 Favours [experimental] Odds IV, Fixed	10     100     Favours (control)     Ratio     .95% CI
Total (95% CI) Heterogeneity: Chi <sup>P</sup> = 21.78, Test for overall effect. Z = 11 Test for subarouo difference C Study or Subgroup logf 1.7.1 CAM Jung,2015 Leung,2011 Nomura,2019 Susano.2020	df = 17 (P = 0.19) .06 (P < 0.00001) s: Chi <sup>2</sup> = 7.78. df = .00dds Ratio1 1.6194 0.56 0.6098 0.21 1.8421 0.85 1.8421 0.61	100.0% ;  ° = 22% = 4 (P = 0.10) SE Weight 028 1.8% 766 8.2% 554 0.9% 95 1.6%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio M. Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.31 [1.18, 33.74] 6.60 [1.18, 22, 23]	0.01 0.1 Favours [experimental] Odds IV. Fixed	10 100 Favours (control) Ratio .95% CI
Total (95% CI) Heterogeneily: Chi <sup>P</sup> = 21.78, Test for overall effect: Z = 11 Test for subaroup difference C Study or Subgroup logf 1.7.1 CAM Jung,2015 Leung,2011 Nomura,2019 Susano,2020 Tsal,2022	df = 17 (P = 0.19) .06 (P < 0.00001) se: Chi <sup>2</sup> = 7.78. df = <b>Odds Ratiol</b> 1.6194 0.56 0.6098 0.22 1.8421 0.84 1.8871 0.84 1.0543 0.5	<b>100.0%</b> ; <b>P</b> = 22% = 4 ( <b>P</b> = 0.10) <b>SE Weight</b> 028 1.8% 766 8.2% 0554 0.9% 195 1.6%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio M. Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.31 [1.18, 33.74] 6.60 [1.96, 22.23] 2.87 [1.05, 7.84]	0.01 0.1 Favours (experimental) Odds IV. Fixed	10 100 Favours [control] Ratio
Total (95% Cl)           Heterogeneity: Chi≅ = 21.78,           Test for overall effect Z = 11           Test for subaroup difference           Image: Ima	df = 17 (P = 0.19) .06 (P < 0.00001) s: ChP = 7.78. df = 1.6194 0.51 0.6098 0.22 1.8421 0.84 1.8421 0.84 1.0543 0.54	100.0% ;  F = 22% = 4 (P = 0.10) SE Weight 328 1.8% 766 8.2% 554 0.9% 195 1.6% 513 2.4% 14.8%	2.40 [2.05, 2.80] F = 48.6% Odds Ratio IV. Fixed, 95% CI 5.05 [1.68, 16.14] 1.84 [1.07, 3.16] 6.31 [1.18, 33.74] 6.60 [1.96, 22.23] 2.87 [1.05, 7.84] 2.76 [1.84, 4.12]	0.01 0.1 Favours (experimental) Odds IV. Fixed	10     100     Favours (control)     Ratio
Total (95% Cl)           Heterogeneity: Chi™ = 21.78,           Test for overall effect. Z = 11           Test for subgroup difference           C           Study or Subgroup logit           1.7.1 CAM           Jung,2015           Leung,2011           Nomura,2019           Susano,2020           Tsai,2022           Subtotal (95% Cl)           Heterogeneity: Chi™ = 6.11, c	df = 17 (P = 0.19) .06 (P < 0.00001) bs: Chi <sup>#</sup> = 7.78. df = .06048 Ratiol 1.6194 0.51 0.6098 0.21 1.8421 0.84 1.8671 0.64 1.0543 0.1 df = 4 (P = 0.19); P df = 4 (P = 0.19); P	100.0% ;  F = 22% = 4 (P = 0.10) SE Weight 328 1.8% 766 8.2% 754 0.9% 195 1.6% 513 2.4% 14.8% = 35%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio IV, Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.31 [1.18, 3.37] 6.30 [1.96, 22.23] 2.87 [1.05, 7.84] 2.76 [1.84, 4.12]	0.01 0.1 Favours (experimental) Odds IV, Fixed	10     100     Favours [control]     Ratio .95% Cl
Total (95% CI) Heterogeneily: Chi <sup>P</sup> = 21.78, Test for overall effect. Z = 11 Test for subgroup logi 1.7.1 CAM Jung,2015 Leung,2011 Nomura,2019 Susano,2020 Tsai,2022 Subtotal (95% CI) Heterogeneily: Chi <sup>P</sup> = 6.11, c Test for overall effect Z = 4.50	df = 17 (P = 0.19) .06 (P < 0.00001) .05 (P < 0.00001) .06 (P < 0.00001) .06 (P < 0.00001) .06 (P < 0.0001) .05 (P = 0.19); P 24 (P < 0.00001)	100.0% ; I <sup>2</sup> = 22% = 4 (P = 0.10) <u>SE Weight</u> 328 1.8% 766 8.2% 766 8.2% 554 0.9% 195 1.6% 513 2.4% 14.8% = 35%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio IV, Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.31 [1.18, 33.74] 2.87 [1.05, 7.84] 2.76 [1.84, 4.12]	0.01 0.1 Favours (experimental) Odds IV, Fixed	10 100 Favours (control) Ratio .95% CI
Total (95% CI) Heterogeneily: Chi <sup>P</sup> = 21.78, Test for overall effect: Z = 11 Test for subgroup difference Study or Subgroup logf 1.7.1 CAM Jung,2015 Leung,2011 Nomura,2019 Susano,2020 Tsal,2022 Subtotal (95% CI) Heterogeneily: Chi <sup>P</sup> = 6.11, c Test for overall effect: Z = 4.9 1.7.2 CAM-ICU	df = 17 (P = 0.19) .06 (P < 0.00001) .05 (P < 0.0001) .06 (P < 0.0001) .06 (P < 0.0001) .06 (P < 0.00001) .07 = 0.19); P .04 (P < 0.00001)	100.0%  F = 22% = 4 (P = 0.10) SE Weight 328 1.8% 766 8.2% 564 0.9% 195 1.6% 513 2.4% 14.8% = 35%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio N.Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.37 [1.18, 33.74] 6.30 [1.9, 3.74] 2.87 [1.05, 7.84] 2.76 [1.84, 4.12]	0.01 0.1 Favours [experimental] Odds IV, Fixed	10 100 Favours [control] Ratio
Total (95% CI) Heterogeneity: Chi <sup>27</sup> = 21.78, Test for overall effect Z = 11 Test for subaroup difference Study or Subaroup logi 1.7.1 CAM Jung,2015 Leung,2015 Leung,2011 Nomura,2019 Susano,2020 Tsal,2022 Subtotal (95% CI) Heterogeneity: Chi <sup>27</sup> = 6.11, c Test for overall effect Z = 4.5 1.7.2 CAM-ICU Mahanna,2020	df = 17 (P = 0.19) .06 (P < 0.0001) s: Chi <sup>#</sup> = 7.78. df = (Odds Ratiol 1.6194 0.50 0.6098 0.21 1.8421 0.84 1.8671 0.64 1.0543 0.4 1.0543 0.4 4 (P < 0.00001) 0.9933 0.50	100.0% F = 22% = 4 (P = 0.10) SE Weight 328 1.8% 766 8.2% 554 0.9% 14.8% = 35% 14.8% = 35%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio IV. Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.31 [1.18, 3.16] 6.31 [1.18, 3.17] 2.87 [1.09, 7.84] 2.76 [1.84, 4.12] 2.70 [1.00, 7.29]	0.01 0.1 Favours (experimental) Odds IV. Fixed	10 100 Favours (control) Ratio
Total (95% Cl)           Heterogeneily: Chi™= 21.78,           Test for overall effect. Z = 11           Test for subgroup logit           Jung,2015           Leung,2015           Suborg,2015           Subgroup,2015           Subgroup,2015           Subgroup,2017           Subgroup,2018           Subgroup,2019           Subgroup,2010           Test for overall effect. Z = 4.511, c           Test for overall effect. Z = 4.52           1.7.2 CAM-ICU           Mahanna,2020           Mauri,2021	df = 17 (P = 0.19) .06 (P < 0.00001) bs: Chi <sup>#</sup> = 7.78. df = .06048 Ratiol 1.6194 0.51 0.6098 0.21 1.8421 0.84 1.8871 0.86 1.0543 0.4 1.8571 0.86 1.0543 0.4 .0543 0.4 .0543 0.4 .0543 0.4 .0543 0.4 .0543 0.5 .000001) 0.9933 0.56 .14609 0.32 .0540 0.22 .0540 0.22	100.0%  F = 22% = 4 (P = 0.10) SE Weight 328 1.8% 768 8.2% 14.8% = 35% 14.8% 14.8% = 35%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio IV, Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.31 [1.18, 3.63] 2.37 [1.05, 7.84] 2.76 [1.84, 4.12] 2.70 [1.00, 7.28] 4.31 [2.37, 7.44] 2.41 [2.37, 7.44]	0.01 0.1 Favours (experimental) Odds IV. Fixed	10 100 Favours [control] Ratio .95% Cl
Total (95% CI) Heterogeneily: Chi <sup>P</sup> = 21.78, Test for overall effect: Z = 11 Test for subgroup logi 1.7.1 CAM Jung.2015 Leung.2011 Nomura.2019 Subtotal (95% CI) Heterogeneily: Chi <sup>P</sup> = 6.11, ci Test for overall effect: Z = 4.5 1.7.2 CAM-ICU Mahanna.2020 Mauri.2021 Ogata,2022 Subtotal (95% CI)	df = 17 (P = 0.19) .06 (P < 0.00001) .05 (P < 0.00001) .06 (P < 0.00001) .06 (P < 0.00001) 1.6194 0.51 0.6098 0.22 1.8421 0.63 1.8421 0.63 1.8421 0.63 1.8421 0.63 1.9543 0.5 1.9543 0.5 0.9933 0.51 1.4609 0.33 0.9123 0.30	100.0% F = 22% = 4 (P = 0.10) SE Weight 328 1.8% 766 8.2% 754 0.9% 195 1.6% 14.8% = 35% 326 2.4% 516 6.7% 15.9%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio IV, Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.31 [1.18, 33.74] 6.31 [1.18, 33.74] 2.87 [1.05, 7.84] 2.76 [1.84, 4.12] 2.70 [1.00, 7.29] 4.31 [2.37, 7.84] 2.49 [1.37, 4.53] 3.18 [2.16, 4.69]	0.01 0.1 Favours (experimental) Odds IV, Fixed	10 100 Favours (control) Ratio .95% CI
Total (95% CI) Heterogeneity: Chi <sup>P</sup> = 21.78, Test for overall effect. Z = 11 Test for subgroup logi 1.7.1 CAM Jung,2015 Leung,2011 Nomura,2019 Susano,2020 Tsai,2022 Subtotal (95% CI) Heterogeneity: Chi <sup>P</sup> = 6.11, c Test for overall effect. Z = 4.9 1.7.2 CAM-ICU Mahanna,2020 Mauri,2021 Ogata,2022 Subtotal (95% CI) Heterogeneity: Chi <sup>P</sup> = 1.74. c	df = 17 (P = 0.19) .06 (P < 0.0001) s: Chi <sup>#</sup> = 7.78. df = (Odds Ratiol 1.6194 0.51 0.6098 0.21 1.8421 0.84 1.8471 0.84 1.8471 0.84 1.0543 0.45 df = 4 (P = 0.19); P 44 (P < 0.00001) 0.9933 0.51 1.4609 0.31 0.9123 0.31 df = 2 (P = 0.42); P	100.0%  F = 22% = 4 (P = 0.10) SE Weight 228 1.8% 766 8.2% 766 8.2% 767 8.2% 767 8.2% 767 8.2% 767 8.2% 767 8.2% 767 8.2% 767 8.2% 7	2.40 [2.05, 2.80] P = 48.6% Odds Ratio M. Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.80 [1.96, 22.23] 2.87 [1.05, 7.28] 2.70 [1.00, 7.29] 4.31 [2.37, 7.84] 2.49 [1.37, 7.84] 3.18 [2.16, 4.69]	0.01 0.1 Favours (experimental) Odds IV. Fixed	10 100 Favours [control] Ratio
Total (95% CI) Heterogeneity: Chi <sup>27</sup> = 21.78, Test for overall effect Z = 11 Test for subgroup logf 1.7.1 CAM Jung,2015 Leung,2011 Nomura,2019 Susano,2020 Tsai,2022 Subtotal (95% CI) Heterogeneity: Chi <sup>27</sup> = 6.11, c Test for overall effect Z = 4.5 1.7.2 CAM-ICU Mahanna,2020 Mauri,2021 Ogata,2022 Subtotal (95% CI) Heterogeneity: Chi <sup>27</sup> = 1.74, c Test for overall effect Z = 5.5	df = 17 (P = 0.19) .06 (P < 0.0001) s: Chi <sup>#</sup> = 7.78. df = <u>(Odds Ratiol</u> 1.6194 0.51 0.6098 0.21 1.8421 0.84 1.8671 0.64 1.0543 0.4 1.0543 0.4 1.0543 0.4 1.0543 0.4 1.4609 0.31 0.9123 0.31 0.9123 0.31 1.4609 0.22 1.4609 0.23 0.9123 0.31 1.4609 0.23 0.9123 0.31 0.9123 0.31 1.926 0.32 0.9123 0.31 1.926 0.32 1.926 0.325 1.926 0.355 1.926 0.3	100.0%  F = 22% = 4 (P = 0.10) SE Weight 328 1.8% r66 8.2% 554 0.9% 14.8% 151 2.4% 14.8% 14.8% 151 6.7% 164 6.7% 15.9% = 0%	2.40 (2.05, 2.80) P = 48.6% Odds Ratio IV, Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.35 [1.18, 3.16] 6.36 [1.18, 3.16] 2.87 [1.05, 7.84] 2.76 [1.84, 4.12] 2.70 [1.00, 7.29] 4.31 [2.37, 8.43] 3.18 [2.16, 4.69]	0.01 0.1 Favours (experimental) Odds IV. Fixed	10     100     Favours (control)     Ratio
Total (95% Cl)           Heterogeneity: Chi™= 21.78, Test for overall effect Z = 11           Test for subgroup         Idifference           Image: I	df = 17 (P = 0.19) .06 (P < 0.00001) s: Chi <sup>#</sup> = 7.78. df = .06dds Ratiol 1.6194 0.56 0.6098 0.27 1.8421 0.84 1.8871 0.67 1.0543 0.4 1.8871 0.67 1.0543 0.4 1.8471 0.87 1.0543 0.4 1.8471 0.87 1.0543 0.4 1.609 0.33 0.9123 0.30 df = 2 (P = 0.42); P 33 (P < 0.00001)	100.0%  F = 22% = 4 (P = 0.10) SE Weight 328 1.8% 766 8.2% 574 0.9% 195 1.6% 195 1.6% 195 1.6% 14.8% = 35% 10.6% 10.0% 10	2.40 (2.05, 2.80) P = 48.6% Odds Ratio <u>IV, Fixed, 95% CI</u> 5.05 (1.58, 16.14) 1.84 (1.07, 3.16) 6.31 (1.14, 3.17) 6.60 (1.96, 22.23) 2.87 (1.05, 7.84) 2.76 (1.84, 4.12) 2.70 (1.00, 7.29) 4.31 (2.37, 7.84) 2.49 (1.37, 4.53) 3.18 (2.16, 4.69)	0.01 0.1 Favours (experimental) Odds IV, Fixed	10 100 Favours [control] Ratio
Total (95% CI) Heterogeneily: Chi <sup>P</sup> = 21.78, Test for overall effect. Z = 11 Test for subgroup logi 1.7.1 CAM Jung,2015 Leung,2011 Nomura,2019 Sustano,2020 Tsai,2022 Subtotal (95% CI) Heterogeneily: Chi <sup>P</sup> = 6.11, ci Test for overall effect. Z = 4.5 1.7.2 CAM-ICU Mahanna,2020 Mauri,2021 Ogata,2022 Subtotal (95% CI) Heterogeneily: Chi <sup>P</sup> = 1.74, ci Test for overall effect. Z = 5.6 1.7.3 Others Chen 2021	df = 17 (P = 0.19) .06 (P < 0.0001) .05 (P < 0.0001) .06 (P < 0.0001) 1.6194 0.51 0.6098 0.22 1.8421 0.84 1.8271 0.61 1.0543 0.5 1.6543 0.5 1.4549 0.31 0.9123 0.31 1.4509 0.33 0.9123 0.31 df = 2 (P = 0.42); P 33 (P < 0.00001)	100.0% P = 22% = 4 (P = 0.10) SE Weight 228 1.8% 768 8.2% 554 0.9% 14.8% 14.8% = 35% 168 2.4% 151 6.7% 168 6.7% 15.9% = 0%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio IV, Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.31 [1.18, 33.74] 2.680 [1.96, 22.23] 2.87 [1.05, 7.84] 2.70 [1.00, 7.29] 4.31 [2.37, 7.84] 2.49 [1.37, 4.53] 3.18 [2.16, 4.69] 3.31 [1.94, 6.74]	0.01 0.1 Favours (experimental) Odds IV, Fixed	10 100 Favours [control] Ratio
Total (95% Cl)           Heterogeneity: Chi <sup>™</sup> = 21.78, Test for overall effect Z = 11. Test for subaroud difference           Itest for subaroup         logit           1.7.1 CAM         Jung,2015           Leung,2011         Nomura,2019           Subarout difference         Subarout difference           Subarout difference         Subarout difference           Image: Subarout difference         Image: Subarout difference           Jung,2015         Leung,2011           Nomura,2019         Susano,2020           Tsai,2022         Subtotal (95% Cl)           Heterogeneity: Chi <sup>™</sup> = 6.11, c         Test for overall effect Z = 4.5           1.7.2 CAM-ICU         Mahanna,2020           Mauri,2021         Ogata,2022           Subtotal (95% Cl)         Heterogeneity: Chi <sup>™</sup> = 1.74, c           Heterogeneity: Chi <sup>™</sup> = 1.74, c         Test for overall effect Z = 5.8           1.7.3 Others         Chen,2021	df = 17 (₽ = 0.19) .06 (P < 0.0001) s: Chi <sup>#</sup> = 7.78. df = 1.8194 0.51 0.6098 0.21 1.8421 0.84 1.8421 0.84 1.8441 0.8441 0.84 1.8441 0.8441	100.0%            F = 22%           = 4 (P = 0.10)           SE         Weight           228         1.8%           228         1.8%           228         1.8%           201         1.3%           228         1.8%           201         1.6%           513         2.4%           5516         6.7%           5516         6.7%           5516         6.7%           5516         6.7%           5516         6.7%           5516         6.7%           5516         6.7%           5516         6.7%           5516         6.7%           5516         6.7%           5516         6.7%           5517         5.0%           505         6.0%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio IV. Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.60 [1.96, 22.23] 2.87 [1.05, 7.28] 2.76 [1.84, 4.12] 2.70 [1.00, 7.29] 4.31 [2.37, 7.84] 3.18 [2.16, 4.69] 3.31 [1.91, 5.74] 3.64 [1.66, 4.20]	0.01 0.1 Favours (experimental) Odds IV. Fixed	
Total (95% Cl)           Heterogeneity: Chi™= 21.78, Test for overall effect Z = 11           Test for subgroup           Image: Study of Subgroup           Jung, 2015           Leung, 2011           Normura, 2019           Subgroup           Susano, 2020           Tsai, 2022           Subtotal (95% Cl)           Heterogeneity: Chi™= 6.11, c           Test for overall effect Z = 4.9           1.7.2 CAM-ICU           Mahana, 2020           Subtotal (95% Cl)           Heterogeneity: Chi™= 1.74, c           Test for overall effect Z = 5.8           1.7.2 CAM-ICU           Mahana, 2020           Mauri, 2021           Ogata, 2022           Subtotal (95% Cl)           Heterogeneity: Chi™= 1.74, c           Test for overall effect Z = 5.8           1.7.3 Others           Chen, 2021           Chen, 2021           Evered, 2020	df = 17 (P = 0.19) .06 (P < 0.00001) es: Chi <sup>#</sup> = 7.78. df = .06dds Ratiol 1.6194 0.56 0.6098 0.27 1.8421 0.84 1.8371 0.67 1.0543 0.51 1.0543 0.51 1.0543 0.51 1.4609 0.33 0.9123 0.36 1.4609 0.33 0.9123 0.36 1.4609 0.33 0.9123 0.36 1.4609 0.22 0.9708 0.22 0.6931 0.22 0.595 0.5	100.0%             F  = 22%           = 4 (P = 0.10)           SE         Weight           328         1.8%           766         8.2%           554         0.9%           195         1.6%           513         2.4%           151         6.7%           156         6.7%           158         6.7%           159%         15.9%           305         8.0%           305         8.0%           305         1.2%           305         7           305         7	2.40 [2.05, 2.80] P = 48.6% Odds Ratio IV, Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.31 [1.18, 3.67] 6.31 [1.18, 3.67] 2.76 [1.84, 4.12] 2.70 [1.00, 7.29] 4.31 [2.37, 8.43] 3.18 [2.16, 4.69] 3.31 [1.91, 5.74] 2.40 [1.36, 3.17]	0.01 0.1 Favours (experimental) Odds IV. Fixed	10     100     Favours (control)     Ratio
Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 21.78, Test for overall effect. Z = 11 Test for subgroup logi 1.7.1 CAM Jung,2015 Leung,2011 Nomura,2019 Susano,2020 Tsai,2022 Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 6.11, of Test for overall effect. Z = 4.9 1.7.2 CAM-ICU Mahanna,2020 Mauri,2021 Ogata,2022 Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = 1.74, of Test for overall effect. Z = 5.8 1.7.3 Others Chen,2021 Chen,2021 Evered,2020 Evered,2020	df = 17 (P = 0.19) .06 (P < 0.00001) bs: Chi <sup>#</sup> = 7.78. df = .06048 Ratiol 1.6194 0.51 0.6098 0.21 1.8421 0.84 1.8871 0.87 1.0543 0.4 1.8871 0.87 1.0543 0.4 1.8471 0.87 1.0543 0.4 1.4609 0.33 0.9123 0.31 df = 2 (P = 0.42); P 33 (P < 0.00001) 1.1969 0.22 0.9708 0.22 0.931 0.22 0.4055 0.11	100.0% F = 22% = 4 (P = 0.10) SE Weight 328 1.8% 766 8.2% 574 0.9% 195 1.6% 513 2.4% 14.8% = 35% 068 2.4% 513 2.4% 14.8% = 35% 068 2.4% 513 2.4% 15.9% = 0% 305 8.0% 305 8.0% 305 11.2% 357 11.3% 368 16.2%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio IV, Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.60 [1.96, 22.23] 2.87 [1.08, 7.84] 2.76 [1.84, 4.12] 2.70 [1.00, 7.28] 4.31 [2.37, 7.84] 2.49 [1.37, 4.53] 3.18 [2.16, 4.69] 3.31 [1.91, 5.74] 2.64 [1.66, 4.20] 2.00 [1.26, 3.17] 2.64 [1.66, 4.20] 2.00 [1.26, 3.17] 3.55 [1.20, 2.21]	0.01 0.1 Favours (experimental) Odds IV. Fixed	10     100     Favours [control]     Ratio     .95% Cl
Total (95% Cl)           Heterogeneity: Chi <sup>™</sup> = 21.78, Test for overall effect Z = 11. Test for subaroud difference           Image: State	df = 17 (P = 0.19) .06 (P < 0.00001) s: Chi <sup>#</sup> = 7.78. df = 1.6194 0.55 0.6098 0.27 1.8421 0.84 1.8471 0.84 1.8471 0.84 1.0543 0.34 df = 4 (P = 0.19); P 44 (P < 0.00001) 0.9933 0.51 1.4609 0.34 1.4609 0.34 1.4609 0.24 0.9708 0.22 0.6931 0.22 0.4055 0.11 0.8629 0.24 0.4655 0.11 0.8629 0.24 0.4652 0.25 0.4655 0.11 0.4629 0.24 0.4652 0.12 0.4655 0.11 0.4629 0.24 0.4652 0.12 0.4655 0.11 0.4629 0.24 0.4629 0.462 0.4629 0.462 0.4629 0.462 0.4629 0.462 0.4629 0.462 0.4629 0.462 0.4629 0.462 0.4629 0.462 0.4629 0.462 0.4629 0.4629 0.4629 0.4629 0.4629 0.4629 0.4629 0.4629 0.4629 0.4629	100.0% F = 22% = 4 (P = 0.10) SE Weight 228 1.8% 766 8.2% 766 8.2% 766 8.2% 766 8.2% 763 1.8% 764 9.3% 764 9.3% 764 9.3% 764 9.3% 764 9.3% 764 9.3% 764 9.3% 765 9.3% 765 9.3% 765 9.3% 765 9.3% 765 9.3% 765 9.3% 765 9.3% 765 9.3% 765 9.3% 765 9.3% 765 9.3% 765 9.5% 765 9.5% 76	2.40 [2.05, 2.80] P = 48.6% Odds Ratio M. Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.80 [1.98, 22.37] 2.87 [1.05, 7.28] 2.70 [1.00, 7.29] 4.31 [2.37, 7.84] 2.70 [1.00, 7.29] 4.31 [2.37, 7.84] 3.31 [2.16, 4.69] 3.31 [1.91, 5.74] 2.64 [1.66, 4.20] 2.00 [1.26, 3.71] 2.37 [1.2, 5.01] 2.37 [1.2, 5.01] 3.31 [2.37, 5.3] 3.31 [2.37	0.01 0.1 Favours (experimental) Odds IV. Fixed	10     100     Favours (control)     100     Ratio
Total (95% Cl)           Heterogeneity: Chi™= 21.78, Test for overall effect Z = 11           Test for subgroup         Ioff           Jung,2015         Jung,2015           Leung,2011         Nomura,2019           Susano,2020         Tsai,2022           Subtotal (95% Cl)         Heterogeneity: Chi™= 6.11, c           Test for overall effect Z = 4.5         1.7.2 CAM-ICU           Mahana,2020         Mauri,2021           Ogata,2022         Subtotal (95% Cl)           Heterogeneity: Chi™= 1.74, ct         Test for overall effect Z = 5.6           1.7.3 Others         Chen,2021           Cher,2021         Cloud           Evered ,2020         Evered ,2020           Evered ,202	df = 17 (P = 0.19) .06 (P < 0.0001) s: Chi <sup>#</sup> = 7.78. df = 1.6194 0.51 0.6098 0.21 1.8421 0.84 1.8671 0.64 1.0543 0.4 1.0543 0.4 1.0543 0.4 df = 4 (P = 0.19); P 44 (P < 0.0001) 0.9933 0.51 1.4609 0.31 0.9123 0.31 0.9123 0.31 df = 2 (P = 0.42); P 33 (P < 0.00001) 1.1969 0.22 0.6931 0.	100.0%  F = 22% = 4 (P = 0.10) SE Weight 328 1.8% 766 8.2% 574 0.9% 14.8% 151 6.7% 14.8% 151 6.7% 154 0.7% 14.8% 153 2.4% 15.9% = 0%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio IV. Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.33 [1.18, 3.16] 6.33 [1.18, 3.16] 2.87 [1.05, 7.84] 2.76 [1.84, 4.12] 2.70 [1.00, 7.29] 4.31 [2.37, 7.84] 2.49 [1.37, 4.53] 3.18 [2.16, 4.69] 3.31 [1.91, 5.74] 2.37 [1.12, 5.01] 4.52 [1.65, 12.38] 1.90 [1.02, 2.21] 1.90 [1.02, 2.21] 1.90 [1.02, 2.21] 1.90 [1.02, 2.21] 1.90 [1.02, 1.23]	0.01 0.1 Favours (experimental) Odds IV. Fixed	10     100     Favours (control)     Ratio
Total (95% Cl)           Heterogeneity: Chi™= 21.78, Test for overall effect Z = 11           Test for subgroup         logit           Jung, 2015         Jung, 2015           Leung, 2011         Nomura, 2019           Subtor overall effect Z = 11         Susano, 2020           Tsai, 2022         Subtotal (95% Cl)           Heterogeneity: Chi™ = 6.11, c         Test for overall effect Z = 4.9           1.7.2 CAM-ICU         Mahana, 2020           Mauri, 2021         Ogata, 2022           Subtotal (95% Cl)         Heterogeneity: Chi™ = 1.74, c           Test for overall effect Z = 5.8         1.7.3 Others           Chen, 2021         Evered, 2020           Evered, 2020         Evered, 2020           Itagaki, 2020         Pol, 2011           Evered, 2020         Pol, 2021           Evered, 2020         Evered, 2020           For assawang 2020         Hagaki, 2020	df = 17 (P = 0.19) .06 (P < 0.0001) es: Chi <sup>#</sup> = 7.78. df = (Odds Ratiol 1.6194 0.56 0.6098 0.27 1.8421 0.84 1.8871 0.67 1.0543 0.4 1.8871 0.67 1.8421 0.84 1.8871 0.67 1.943 0.4 1.8471 0.87 1.944 (P < 0.00001) 0.9933 0.56 1.4609 0.33 0.9123 0.30 df = 2 (P = 0.42); P 33 (P < 0.00001) 1.1969 0.22 0.6931 0.22 0.6931 0.22 0.6931 0.22 0.6931 0.22 0.6935 0.57 1.6055 0.57 0.6149 0.33 1.2565 0.57 0.6149 0.32 0.57 0.	100.0%            P = 22%           = 4 (P = 0.10)           SE Weight           328         1.8%           766         8.2%           554         0.9%           151         2.4%           1513         2.4%           1513         2.4%           1514         6.7%           048         6.7%           055         1.1%           305         8.0%           305         8.0%           305         8.0%           305         8.0%           317         11.3%           312         4.3%           312         4.3%	2.40 (2.05, 2.80) P = 48.6% Odds Ratio <u>IV, Fixed, 95% CI</u> 5.05 [1.58, 16.14] 1.84 (1.07, 3.16] 6.60 [1.96, 22.23] 2.87 [1.05, 7.84] 2.76 [1.84, 4.12] 2.70 (1.00, 7.29] 4.31 [2.37, 7.84] 2.49 [1.66, 4.20] 3.31 [1.91, 5.74] 2.00 [1.26, 3.17] 1.50 [1.02, 2.21] 2.37 [1.12, 6.11] 3.57 [1.09, 0.43] 1.50 [0.09, 4.01] 3.57 [1.09, 0.43]	0.01 0.1 Favours (experimental) Odds IV. Fixed	10 100 Favours [control] Ratio
Total (95% CI) Heterogeneily: Chi <sup>2</sup> = 21.78, Test for overall effect. Z = 11 Test for subgroup logi 1.7.1 CAM Jung,2015 Leung,2011 Nomura,2019 Susbotal (95% CI) Heterogeneily: Chi <sup>2</sup> = 6.11, ci Test for overall effect. Z = 4.8 1.7.2 CAM-ICU Mahanna,2020 Mauri,2021 Ogata,2022 Subtotal (95% CI) Heterogeneily: Chi <sup>2</sup> = 1.74, ci Test for overall effect. Z = 5.8 1.7.3 Others Chen,2021 Chen,2021 Evered ,2020 Evered	$\begin{array}{c} df = 17 \ (P = 0.19) \\ .06 \ (P < 0.0001) \\ .05 \ (P < 0.0001) \\ .07 \ (P < 0.0001) \\ .08 \ (P < 0.0001) \\ .098 \ (P < 0.0001) \\ .0993 \ (P < 0.00001) \\ .0993 \ (P < 0$	100.0%           IP = 22%           = 4 (P = 0.10)           SE         Weight           228         1.8%           766         8.2%           554         0.9%           153         2.4%           153         2.4%           154         6.7%           156         6.7%           156         6.7%           156         6.7%           305         8.0%           367         11.2%           368         16.2%           312         4.3%           312         4.3%           312         4.3%           312         4.3%           312         4.3%           312         4.3%           312         4.3%           312         4.3%           312         4.3%           314         1.8%           315         1.3%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio M. Fixed, 95% CI 5.05 [1.68, 16.14] 1.84 [1.07, 3.16] 6.30 [1.18, 16.14] 2.70 [1.00, 7.29] 2.87 [1.05, 7.28] 4.31 [2.37, 7.84] 2.49 [1.37, 7.84] 2.49 [1.37, 7.84] 2.49 [1.37, 4.53] 3.18 [2.16, 4.69] 3.31 [1.91, 5.74] 2.44 [1.66, 4.20] 2.00 [1.26, 3.17] 2.52 [1.65, 12.38] 4.52 [1.55, 12.38] 4.52 [1.55, 12.38] 4.52 [1.55, 12.38] 4.52 [1.65, 12.38] 4.52 [1.65, 12.38] 4.52 [1.09, 11.37] 5.52 [1.09, 11.37	0.01 0.1 Favours (experimental) Odds IV. Fixed	10 100 Favours [control] Ratio
Total (95% Cl)           Heterogeneity: Chi <sup>™</sup> = 21.78, Test for overall effect Z = 11. Test for subaroud difference           Study or Subaroup         log1           1.7.1 CAM         Jung,2015           Leung,2011         Nomura,2019           Subarout (95% Cl)         Heterogeneity: Chi <sup>™</sup> = 6.11, c           Test for overall effect Z = 4.5         1.7.2 CAM-ICU           Manana,2020         Mauri,2021           Ogata,2022         Subtotal (95% Cl)           Heterogeneity: Chi <sup>™</sup> = 1.74, c           Test for overall effect Z = 5.8           1.7.3 Others           Chen,2021           Evered,2020	df = 17 (P = 0.19) .06 (P < 0.0001) .05 (P < 0.0001) .05 (P = 7.78, df = 1.8194 0.51 0.6098 0.21 1.8421 0.84 1.8671 0.64 1.8671 0.64 1.8671 0.64 1.8671 0.64 1.8699 0.32 .0.9933 0.51 1.4609 0.32 0.9933 0.51 1.4609 0.32 0.9933 0.51 1.4609 0.32 0.9933 0.51 1.4609 0.32 0.9933 0.51 1.4609 0.32 0.9933 0.51 1.4609 0.32 0.9933 0.51 1.4609 0.32 0.9938 0.22 0.6931 0.22 0.5951 0.22 0.5951 0.22 0.5951 0.22 0.5951 0.25 0.55	100.0%           IP = 22%           = 4 (P = 0.10)           SE         Weight           328         1.8%           328         1.8%           328         1.8%           313         2.4%           551         5.7%           3068         2.4%           355         15.9%           305         8.0%           305         1.12%           305         1.12%           305         1.12%           312         4.3%           312         4.3%           312         4.3%           312         4.3%           312         4.3%           313         1.1%           314         1.3%           315         1.13%           312         4.3%           312         4.3%           312         4.3%           312         4.3%           312         4.3%           312         4.3%           312         4.3%           312         4.3%           312         4.3%           312         4.3%           312	2.40 [2.05, 2.80] P = 48.6% Odds Ratio IV. Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.60 [1.96, 22.23] 2.87 [1.05, 7.34] 2.76 [1.84, 4.12] 2.70 [1.00, 7.29] 4.31 [2.37, 7.84] 2.49 [1.37, 4.53] 3.18 [2.16, 4.69] 3.31 [1.91, 5.74] 2.64 [1.66, 4.20] 2.00 [1.26, 3.17] 1.50 [1.25, 21.39] 3.49 [1.37, 4.51] 3.49 [1.37, 4.53] 3.18 [2.16, 4.69] 3.31 [1.91, 5.74] 3.52 [1.09, 11.37] 3.49 [1.06, 11.49] 3.52 [1.00, 3.12] 3.52 [1.06, 11.49] 3.52 [1.06, 11.49] 3.53 [1.52 [1.06, 11.49] 3.54 [1.52 [1.06, 11.49] 3.54 [1.52 [1.06, 11.49] 3.54 [1.52 [1.06, 11.49] 3.55 [1.52 [	0.01 0.1 Favours (experimental) Odds IV. Fixed	10     100     Favours (control)     Ratio     .95% Cl
Total (95% Cl)           Heterogeneity: Chi™= 21.78, Test for overall effect Z = 11           Test for subgroup         logf           Itest for subgroup         logf           1.7.1 CAM         Jung, 2015           Leung, 2011         Nomura, 2019           Susano, 2020         Tsai, 2022           Subtotal (95% Cl)         Heterogeneity: Chi™= 6.11, c           1.7.2 CAM-ICU         Mahana, 2020           Mauri, 2021         Ogata, 2022           Subtotal (95% Cl)         Heterogeneity: Chi™= 1.74, c           Test for overall effect Z = 4.5         1.7.3 Others           Chen, 2021         Cy20           Evered, 2020         Evered, 2020           Evered, 2020         Evered, 2020           Evered, 2020         Evered, 2020           Evered, 2020         Evered, 2020           Suber, 2021         Collagaki, 2020           Folgent, 2021         Evered, 2020           Suber, 2022         Subtotal (95% Cl)	df = 17 (P = 0.19) .06 (P < 0.00001) s: Chi <sup>#</sup> = 7.78. df = <u>Odds Ratiol</u> 1.6194 0.51 0.6098 0.22 1.8421 0.84 1.8871 0.6' 1.0543 0.4' 1.943 0.51 1.4609 0.31 0.9123 0.31 df = 2 (P = 0.42); P 33 (P < 0.00001) 1.1968 0.22 0.6931 0.22 0.6935 0.57 0.6419 0.33 1.2585 0.57 0.6419 0.33 1.2588 0.57 0.6419 0.33 1.2588 0.57 0.6419 0.33 1.2588 0.57 0.6419 0.33 1.2588 0.57 0.6588 0.27 0.5888 0.27 0.5988 0.57 0.5988 0.57 0.598	$\begin{array}{c} 100.0\% \\    F = 22\% \\ \\ = 4 (P = 0.10) \\ \hline SE \ Weight \\ \\ 328 \ 1.8\% \\ 666 \ 8.2\% \\ 576 \ 0.9\% \\ 14.8\% \\ = 35\% \\ \hline \\ 151 \ 2.4\% \\ 151 \ 6.7\% \\ 14.8\% \\ = 35\% \\ \hline \\ 3068 \ 2.4\% \\ 15.9\% \\ = 0\% \\ \hline \\ 305 \ 8.0\% \\ 305 \ 8.0\% \\ 305 \ 11.2\% \\ 3068 \ 16.2\% \\ 312 \ 4.3\% \\ 312 \ 4.3\% \\ 312 \ 4.3\% \\ 312 \ 4.3\% \\ 308 \ 1.8\% \\ 308 \ 1.7\% \\ 578 \ 8.2\% \\ 502 \ 1.7\% \\ 588 \ 2.4\% \\ 502 \ 1.7\% \\ 588 \ 2.4\% \\ 502 \ 1.7\% \\ 588 \ 2.4\% \\ 502 \ 1.7\% \\ 588 \ 2.4\% \\ 502 \ 1.7\% \\ 588 \ 2.4\% \\ 502 \ 1.7\% \\ 588 \ 2.4\% \\ 502 \ 1.7\% \\ 588 \ 2.4\% \\ 502 \ 1.7\% \\ 588 \ 2.4\% \\ 502 \ 1.7\% \\ 588 \ 2.4\% \\ 502 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.7\% \\ 580 \ 2.4\% \\ 500 \ 1.1\% \\ 580 \ 2.4\% \\ 580 \ $	2.40 [2.05, 2.80] P = 48.6% Odds Ratio IV, Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.31 [1.18, 3.16] 2.76 [1.84, 4.12] 2.76 [1.84, 4.12] 2.70 [1.00, 7.29] 4.31 [2.37, 7.84] 2.49 [1.37, 4.53] 3.18 [2.16, 4.69] 3.31 [1.91, 5.74] 2.37 [1.12, 5.01] 4.52 [1.65, 12.38] 1.80 [0.90, 4.01] 4.52 [1.65, 12.38] 1.80 [0.90, 4.01] 4.52 [1.65, 12.38] 1.80 [0.90, 4.01] 4.52 [1.65, 12.38] 1.80 [0.90, 4.01] 4.52 [1.65, 12.38] 1.81 [0.90, 11.37] 3.48 [1.06, 3.12] 2.18 [1.81, 2.63]	0.01 0.1 Favours (experimental) Odds IV. Fixed	
Total (95% CI)           Heterogeneity: Chii <sup>2</sup> = 21.78, Test for overall effect Z = 11           Test for subgroup left           Iterogeneity: Chi <sup>2</sup> = 0.178, Jung, 2015           Leung, 2011           Nomura, 2019           Susano, 2020           Tsal, 2022           Subtotion (95% CI)           Heterogeneity: Chi <sup>2</sup> = 6.11, c           Test for overall effect Z = 4.9           1.7.2 CAM-ICU           Mahana, 2020           Mauri, 2021           Ogata, 2022           Subtotal (95% CI)           Heterogeneity: Chi <sup>2</sup> = 1.74, c           Test for overall effect Z = 5.8           1.7.3 Others           Chen, 2021           Evered, 2020           Goudzwaard, 2020           Itagaki, 2020           Pol, 2011           Roopas awang, 2020           Sieber, 2022           Xiang, 2022           Subtotal (95% CI)           Heterogeneity: Chi <sup>2</sup> = 1.0.47, for	df = 17 (P = 0.19) .06 (P < 0.0001) es: Chi <sup>#</sup> = 7.78. df = (Odds Ratiol 1.6194 0.56 0.6098 0.21 1.8421 0.84 1.8671 0.67 1.0543 0.4 1.8471 0.87 1.0543 0.4 1.8471 0.87 1.0543 0.4 1.8471 0.87 1.0543 0.4 1.947 0.67 1.4609 0.31 0.9123 0.36 1.4609 0.31 0.9123 0.36 1.4609 0.22 0.9708 0.22 0.6931 0.22 0.6931 0.22 0.6931 0.22 0.6938 0.22 1.2565 0.55 1.2499 0.4 0.5988 0.21 0.5988 0.21 0.69 0.21 0.5988 0.21 0.5988 0.21 0.69 0.21 0.5988 0.21 0.5	100.0%               = 22%           = 4 (P = 0.10)           SE         Weight           328         1.8%           766         8.2%           554         0.9%           151         2.4%           1513         2.4%           1513         2.4%           1514         6.7%           048         6.7%           055         8.0%           305         8.0%           305         8.0%           305         11.2%           324         4.3%           312         4.3%           312         4.3%           3141         1.8%           3088         1.7%           578         8.2%           69.2%         754	2.40 (2.05, 2.80) P = 48.6% Odds Ratio IV, Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 (1.07, 3.16] 6.60 [1.96, 22.23] 2.87 [1.05, 7.84] 2.70 [1.00, 7.29] 4.31 [2.37, 7.84] 2.40 [1.84, 4.12] 2.70 [1.00, 7.29] 4.31 [2.37, 7.84] 2.41 [2.37, 7.84] 2.43 [2.37, 7.84] 2.44 [1.66, 4.20] 3.31 [1.91, 5.74] 2.46 [1.66, 4.20] 3.31 [1.91, 5.74] 1.52 [1.09, 11.37] 3.49 [1.06, 11.49] 1.82 [1.00, 3.12] 2.18 [1.81, 2.63]	0.01 0.1 Favours (experimental) Odds IV. Fixed	
Total (95% Cl)           Heterogeneity: Chi <sup>™</sup> = 21.78, Test for overall effect Z = 11           Test for subaroud difference           Image: Im	df = 17 (P = 0.19) .06 (P < 0.0001) s: Chi <sup>#</sup> = 7.78. df = 1.6194 0.51 0.6098 0.22 1.8421 0.84 1.8471 0.84 1.8471 0.84 1.0543 0.34 df = 4 (P = 0.19); P 44 (P < 0.00001) 0.9933 0.51 1.4609 0.34 1.4609 0.34 0.9123 0.33 df = 2 (P = 0.42); P 33 (P < 0.00001) 1.1969 0.22 0.6931 0.22 0.6931 0.22 0.6931 0.22 0.6931 0.23 1.5085 0.15 0.6414 9 0.34 1.2585 0.54 1.2499 0.4 0.5988 0.23 .249 0.4 0.5988 0.23 .24 (P < 0.00001)	100.0%           IP = 22%           = 4 (P = 0.10)           SE         Weight           228         1.8%           766         8.2%           766         8.2%           768         8.2%           768         8.2%           768         8.2%           768         8.2%           768         8.2%           768         8.2%           756         8.0%           305         8.0%           305         8.0%           324         4.3%           324         4.3%           324         4.3%           324         1.8%           321         4.3%           321         4.3%           321         4.3%           324         4.3%           321         4.3%           758         8.2%           69.2%         = 14%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio M. Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.80 [1.98, 22.37, 2.87 [1.05, 7.28] 4.31 [2.18, 3.74] 2.76 [1.84, 4.12] 2.70 [1.00, 7.29] 4.31 [2.37, 7.84] 2.43 [1.23, 7.84] 2.43 [1.23, 7.84] 2.44 [1.68, 4.20] 2.00 [1.26, 3.17] 2.37 [1.2, 501] 4.52 [1.65, 1.2.38] 1.50 [1.02, 2.21] 1.50 [1.02, 2.21] 1.50 [1.02, 2.21] 2.37 [1.12, 501] 4.52 [1.05, 1.2.38] 3.48 [1.06, 1.149] 1.82 [1.06, 3.12] 2.18 [1.81, 2.63]	0.01 0.1 Favours (experimental) Odds IV. Fixed	10     100     Favours (control)     100     Ratio     .95% Cl
Total (95% Cl)           Heterogeneity: Chi <sup>™</sup> = 21.78, Test for overall effect Z = 11. Test for suboroup difference           Itest for suboroup difference           Subotal (55% Cl)           Heterogeneity: Chi <sup>™</sup> = 6.11, c           Test for overall effect Z = 4.9           1.7.2 CAM-ICU           Mahana, 2020           Mauri, 2021           Ogata, 2022           Subtotal (95% Cl)           Heterogeneity: Chi <sup>™</sup> = 1.74, c           Test for overall effect Z = 5.8           1.7.3 Others           Chen, 2021           Evered, 2020           Evered, 2020           Evered, 2020           Evered, 2020           Subotal (95% Cl)           Heterogeneity: Chi <sup>™</sup> = 10.47, Test for overall effect Z = 8.2           Total (95% Cl)	df = 17 (P = 0.19) .06 (P < 0.0001) s: Chi <sup>#</sup> = 7.78. df = 1.8194 0.50 0.6098 0.21 1.8421 0.84 1.8671 0.64 1.8671 0.64 1.8671 0.64 1.8671 0.64 1.8671 0.64 1.8699 0.21 0.9933 0.50 1.4609 0.21 0.9933 0.50 1.4609 0.21 0.9933 0.50 1.4609 0.21 0.9938 0.22 0.6931 0.22 0.2931 0.22 0.2931 0.29 0.2931 0.29 0.2941 0.29 0.2941 0.29 0.2941 0.29 0.2941 0.29 0.2941 0.29 0.2941	100.0%             F  = 22%           = 4 (P = 0.10)           SE         Weight           328         1.8%           766         8.2%           513         2.4%           513         2.4%           151         2.4%           154         0.7%           154         6.7%           168         2.4%           154         6.7%           156         1.5%           9068         2.4%           157         1.3%           905         8.0%           905         1.2%           906         1.2%           917         1.13%           918         1.8%           918         1.8%           918         1.8%           918         1.8%           912         4.3%           912         4.3%           912         4.3%           912         4.3%           912         4.3%           912         4.3%           914         1.8%           914         1.4%           914         1.4%           914 <t< td=""><td>2.40 [2.05, 2.80] P = 48.6% Odds Ratio IV. Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.60 [1.96, 22.23] 2.87 [1.05, 7.34] 2.76 [1.84, 4.12] 2.70 [1.00, 7.29] 4.31 [2.37, 7.84] 2.49 [1.37, 4.53] 3.18 [2.16, 4.69] 3.31 [1.91, 5.74] 2.64 [1.66, 4.20] 2.00 [1.26, 3.17] 1.50 [1.02, 1.21] 3.49 [1.37, 4.51] 3.18 [2.16, 4.69] 3.31 [2.16, 4.69] 3.31 [2.16, 1.18] 3.49 [1.06, 1.14] 3.52 [1.09, 11.37] 3.48 [1.06, 1.14] 1.82 [1.06, 3.12] 2.18 [1.81, 2.63] 2.40 [2.05, 2.80]</td><td>0.01 0.1 Favours (experimental) Odds IV. Fixed</td><td>10     100     Favours (control)     Ratio    </td></t<>	2.40 [2.05, 2.80] P = 48.6% Odds Ratio IV. Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.60 [1.96, 22.23] 2.87 [1.05, 7.34] 2.76 [1.84, 4.12] 2.70 [1.00, 7.29] 4.31 [2.37, 7.84] 2.49 [1.37, 4.53] 3.18 [2.16, 4.69] 3.31 [1.91, 5.74] 2.64 [1.66, 4.20] 2.00 [1.26, 3.17] 1.50 [1.02, 1.21] 3.49 [1.37, 4.51] 3.18 [2.16, 4.69] 3.31 [2.16, 4.69] 3.31 [2.16, 1.18] 3.49 [1.06, 1.14] 3.52 [1.09, 11.37] 3.48 [1.06, 1.14] 1.82 [1.06, 3.12] 2.18 [1.81, 2.63] 2.40 [2.05, 2.80]	0.01 0.1 Favours (experimental) Odds IV. Fixed	10     100     Favours (control)     Ratio
Total (95% Cl)           Heterogeneity: Chi™= 21.78, Test for overall effect Z = 11           Test for subgroup         logf           Study or Subgroup         logf           1.7.1 CAM         Jung, 2015           Leung, 2011         Nomura, 2019           Susano, 2020         Tsal, 2022           Subtotal (95% Cl)         Heterogeneity: Chi™= 6.11, c           Test for overall effect Z = 4.9         1.7.2 CAM-ICU           Mahana, 2020         Mauri, 2021           Ogata, 2022         Subtotal (95% Cl)           Heterogeneity: Chi™= 1.74, c         Test for overall effect Z = 5.8           1.7.3 Others         Chen, 2021           Chen, 2021         Evered, 2020           Evered, 2020         Evered, 2020           Subtotal (95% Cl)         Heterogeneity: Chi™ = 1.74, r           Trast for overall effect Z = 5.8         1.7.3 Others           Chen, 2021         Evered, 2020           Evered, 2020         Evered, 2020           Subtotal (95% Cl)         Heterogeneity: Chi™ = 10.47, Test for overall effect Z = 8.2           Total (95% Cl)         Heterogeneity: Chi™ = 10.47, Test for overall effect Z = 21.78, Eventset And State Z = 2	df = 17 (P = 0.19) .06 (P < 0.00001) s: Chi <sup>#</sup> = 7.78. df = <u>Odds Ratiol</u> 1.6194 0.51 0.6098 0.22 1.8421 0.84 1.8871 0.64 1.0543 0.4 1.0543 0.4 1.0543 0.4 df = 4 (P = 0.19); P 44 (P < 0.00001) 0.9933 0.51 1.4609 0.33 0.9123 0.31 df = 2 (P = 0.42); P 33 (P < 0.00001) 1.1969 0.22 0.6931 0.22 0.6938 0.23 1.2685 0.51 1.2499 0.31 0.5988 0.23 0.5988 0.23 21 (P < 0.00001) df = 17 (P = 0.19)	100.0%               = 22%           = 4 (P = 0.10)           SE         Weight           328         1.8%           766         8.2%           513         2.4%           9195         1.6%           513         2.4%           9155         2.6%           9168         2.4%           9159         1.6%           9168         2.4%           9159         9.6%           9168         2.4%           9159         9.6%           9168         1.6%           917         1.1.3%           918         1.6%           912         4.3%           912         4.3%           912         4.3%           913         1.8%           912         4.3%           913         1.8%           92%         F= 14%           100.0%	2.40 [2.05, 2.80] P = 48.6% Odds Ratio IV. Fixed, 95% CI 5.05 [1.58, 16.14] 1.84 [1.07, 3.16] 6.03 [1.18, 3.16] 6.31 [1.18, 3.16] 2.76 [1.84, 4.12] 2.70 [1.00, 7.29] 4.31 [2.37, 8.44] 2.40 [1.37, 4.53] 3.18 [2.16, 4.69] 3.31 [1.91, 5.74] 2.37 [1.12, 5.01] 4.52 [1.65, 12.38] 1.80 [0.90, 4.01] 4.52 [1.65, 12.38] 1.80 [0.90, 4.01] 4.52 [1.65, 12.38] 1.80 [0.90, 4.01] 4.52 [1.65, 12.38] 1.81 [0.90, 11.37] 3.48 [1.81, 2.63] 2.40 [2.05, 2.80]	0.01 0.1 Favours (experimental) Odds IV. Fixed	10     100     Favours (control)     Ratio

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.<sup>[41]</sup> Indeed, several medical societies recommended that frailty should be assessed before surgery in older adults to reduce the incidence of postoperative complications.<sup>[42,43]</sup> 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.

## Financial support and sponsorship

This work was supported by the Key Research and Development Program of Hebei Province (Project number: 19277714D).

#### **Conflicts of interest**

There are no conflicts of interest.

#### REFERENCES

- Rengel KF, Boncyk CS, DiNizo D, Hughes CG. Perioperative neurocognitive disorders in adults requiring cardiac surgery: Screening, prevention, and management. Semin Cardiothorac Vasc Anesth 2023;27:25-41.
- Evered L, Atkins K, Silbert B, Scott DA. Acute peri-operative neurocognitive disorders: A narrative review. Anaesthesia 2022;77 Suppl 1:34-42.
- Choi S, Jung I, Yoo B, Lee S, Kim MC. Risk factors for postoperative delirium in elderly patients after spinal fusion surgery. Anesth Pain Med (Seoul) 2020;15:275-82.
- Evered LA, Chan MT, Han R, Chu MH, Cheng BP, Scott DA, et al. Anaesthetic depth and delirium after major surgery: A randomised clinical trial. Br J Anaesth 2021;127:704-12.
- de la Varga-Martínez O, Gutiérrez-Bustillo R, Muñoz-Moreno MF, López-Herrero R, Gómez-Sánchez E, Tamayo E. Postoperative delirium: An independent risk factor for poorer quality of life with long-term cognitive and functional decline after cardiac surgery. J Clin Anesth 2023;85:111030.
- Li Y, Zhang B. Effects of anesthesia depth on postoperative cognitive function and inflammation: A systematic review and meta-analysis. Minerva Anestesiol 2020;86:965-73.
- Li GH, Zhao L, Lu Y, Wang W, Ma T, Zhang YX, *et al*. Development and validation of a risk score for predicting postoperative delirium after major abdominal surgery by incorporating preoperative risk factors and surgical Apgar score. J Clin Anesth 2021;75:110408.
- Huang H, Lin F, Cen L, Jing R, Pan L. Cancer-related anemia is a risk factor for medium-term postoperative cognitive dysfunction in laparoscopic surgery patients: An observational prospective study. Neural Plast 2020;2020:4847520.
- Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Audisio R, Borozdina A, et al. European society of anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. Eur J Anaesthesiol 2017;34:192-214.
- Sandrucci S. Frailty: How to assess, prognostic role. Eur J Surg Oncol 2024;50:106862.
- Caliskan H, Igdir V, Ozsurekci C, Caliskan E, Halil M. Frailty and sarcopenia in patients with distal radius fracture: A geriatric perspective. Geriatr Orthop Surg Rehabil 2020;11:2151459320906361.

- 12. Sioutas G, Tsoulfas G. Frailty assessment and postoperative outcomes among patients undergoing general surgery. Surgeon 2020;18:e55-66.
- Esmaeeli S, Franco-Garcia E, Akeju O, Heng M, Zhou C, Azocar RJ, et al. Association of preoperative frailty with postoperative delirium in elderly orthopedic trauma patients. Aging Clin Exp Res 2022;34:625-31.
- Chen Y, Qin J. Modified frailty index independently predicts postoperative delirium and delayed neurocognitive recovery after elective total joint arthroplasty. J Arthroplasty 2021;36:449-53.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. PLoS Med 2009;6:e1000100.
- Krewulak KD, Hiploylee C, Ely EW, Stelfox HT, Inouye SK, Fiest KM. Adaptation and validation of a chart-based delirium detection tool for the ICU (CHART-DEL-ICU). J Am Geriatr Soc 2021;69:1027-34.
- 17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-5.
- Tsai CY, Liu KH, Lai CC, Hsu JT, Hsueh SW, Hung CY, *et al.* Association of preoperative frailty and postoperative delirium in older cancer patients undergoing elective abdominal surgery: A prospective observational study in Taiwan. Biomed J 2023;46:100557.
- 19. Xiang D, Xing H, Zhu Y. A predictive nomogram model for postoperative delirium in elderly patients following laparoscopic surgery for gynecologic cancers. Support Care Cancer 2022;31:24.
- Ogata Y, Kobayashi N, Yamauchi M. Investigation of risk factors for postoperative delirium after transcatheter aortic valve implantation: A retrospective study. J Clin Med 2022;11:3317.
- Roopsawang I, Thompson H, Zaslavsky O, Belza B. Predicting hospital outcomes with the reported edmonton frail scale-Thai version in orthopaedic older patients. J Clin Nurs 2020;29:4708-19.
- 22. Itagaki A, Sakurada K, Matsuhama M, Yajima J, Yamashita T, Kohzuki M. Impact of frailty and mild cognitive impairment on delirium after cardiac surgery in older patients. J Cardiol 2020;76:147-53.
- Susano MJ, Grasfield RH, Friese M, Rosner B, Crosby G, Bader AM, et al. Brief preoperative screening for frailty and cognitive impairment predicts delirium after spine surgery. Anesthesiology 2020;133:1184-91.
- Leung JM, Tsai TL, Sands LP. Brief report: Preoperative frailty in older surgical patients is associated with early postoperative delirium. Anesth Analg 2011;112:1199-201.
- Pol RA, van Leeuwen BL, Visser L, Izaks GJ, van den Dungen JJ, Tielliu IF, *et al.* Standardised frailty indicator as predictor for postoperative delirium after vascular surgery: A prospective cohort study. Eur J Vasc Endovasc Surg 2011;42:824-30.
- Jung P, Pereira MA, Hiebert B, Song X, Rockwood K, Tangri N, et al. The impact of frailty on postoperative delirium in cardiac surgery patients. J Thorac Cardiovasc Surg 2015;149:869-75.e1.
- 27. Nomura Y, Nakano M, Bush B, Tian J, Yamaguchi A, Walston J, *et al.* Observational study examining the association of baseline

frailty and postcardiac surgery delirium and cognitive change. Anesth Analg 2019;129:507-14.

- Evered LA, Vitug S, Scott DA, Silbert B. Preoperative frailty predicts postoperative neurocognitive disorders after total hip joint replacement surgery. Anesth Analg 2020;131:1582-8.
- 29. Mahanna-Gabrielli E, Zhang K, Sieber FE, Lin HM, Liu X, Sewell M, *et al.* Frailty is associated with postoperative delirium but not with postoperative cognitive decline in older noncardiac surgery patients. Anesth Analg 2020;130:1516-23.
- 30. Goudzwaard JA, de Ronde-Tillmans MJ, de Jager TA, Lenzen MJ, Nuis RJ, van Mieghem NM, *et al.* Incidence, determinants and consequences of delirium in older patients after transcatheter aortic valve implantation. Age Ageing 2020;49:389-94.
- 31. Mauri V, Reuter K, Körber MI, Wienemann H, Lee S, Eghbalzadeh K, *et al.* Incidence, risk factors and impact on long-term outcome of postoperative delirium after transcatheter aortic valve replacement. Front Cardiovasc Med 2021;8:645724.
- Sieber F, Gearhart S, Bettick D, Wang NY. Edmonton frailty scale score predicts postoperative delirium: A retrospective cohort analysis. BMC Geriatr 2022;22:585.
- Kong H, Xu LM, Wang DX. Perioperative neurocognitive disorders: A narrative review focusing on diagnosis, prevention, and treatment. CNS Neurosci Ther 2022;28:1147-67.
- 34. Tasbihgou SR, Absalom AR. Postoperative neurocognitive disorders. Korean J Anesthesiol 2021;74:15-22.
- Allison R 2<sup>nd</sup>, Assadzandi S, Adelman M. Frailty: Evaluation and management. Am Fam Physician 2021;103:219-26.
- Fabrício DM, Chagas MH, Diniz BS. Frailty and cognitive decline. Transl Res 2020;221:58-64.
- Vatic M, von Haehling S, Ebner N. Inflammatory biomarkers of frailty. Exp Gerontol 2020;133:110858.
- Gracie TJ, Caufield-Noll C, Wang NY, Sieber FE. The association of preoperative frailty and postoperative delirium: A meta-analysis. Anesth Analg 2021;133:314-23.
- 39. Guerci B, Giorgino F, Sapin H, Boye K, Lebrec J, Federici MO, *et al.* The real-world observational prospective study of health outcomes with dulaglutide and liraglutide in patients with type 2 diabetes (TROPHIES): Patient disposition, clinical characteristics and treatment persistence at 12 months. Diabetes Obes Metab 2022;24:2373-82.
- Pozzi M, Mariani S, Scanziani M, Passolunghi D, Bruni A, Finazzi A, et al. The frail patient undergoing cardiac surgery: Lessons learned and future perspectives. Front Cardiovasc Med 2023;10:1295108.
- 41. Hempenius L, Slaets JP, van Asselt D, de Bock GH, Wiggers T, van Leeuwen BL. Outcomes of a geriatric liaison intervention to prevent the development of postoperative delirium in frail elderly cancer patients: Report on a multicentre, randomized, controlled trial. PLoS One 2013;8:e64834.
- 42. Cooper L, Abbett SK, Feng A, Bernacki RE, Cooper Z, Urman RD, et al. Launching a geriatric surgery center: Recommendations from the society for perioperative assessment and quality improvement. J Am Geriatr Soc 2020;68:1941-6.
- 43. Goede V. Frailty and cancer: Current perspectives on assessment and monitoring. Clin Interv Aging 2023;18:505-21.
- 44. Norris CM, Close JC. Prehabilitation for the frailty syndrome: Improving outcomes for our most vulnerable patients. Anesth Analg 2020;130:1524-33.

Supplementary 1	Fable 1: Full search strategy
Database	Keywords
1	("Frail Elderly"[Mesh]) OR "Frailty"[Mesh]
2	(frail[Title/Abstract]) OR (frailty[Title/Abstract])
3	10R2
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])) OR (deliri*[Title/Abs
6	40R5
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	80R9
11	3AND6AND7AND10
Pubmed	348
1	frail: ab, ti OR frailty: ab, ti
2	'frailty'/exp OR 'frail elderly'/exp
3	10R2
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 pod: 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	80R9
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=(POCD)) OR TS=(Declinite)) OR TS=(delirite))
3	(((((((TS=(postoperative)) OR TS=(operation*)) OR TS=(surgery)) OR TS=(anaesthesia)) OR TS=(anesthesia)) 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	D 1
litle	1	Identify the report as a systematic review	Page 1
Abstract	2	ADSIRACI	Page 1
	Ζ		rage i
Pationale	3	Describe the rationale for the raview in the context of existing knowledge	Page 2
Objectives	3 1	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

Supplementary Ta	able 2: Co	ontd	
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