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Systematic Review

Impact of preoperative uni- or multimodal prehabilitation on postoperative morbidity: meta-analysis

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Abstract

Background: Postoperative complications occur in up to 43% of patients after surgery, resulting in increased morbidity and economic burden. Prehabilitation has the potential to increase patients' preoperative health status and thereby improve postoperative outcomes. However, reported results of prehabilitation are contradictory. The objective of this systematic review is to evaluate the effects of prehabilitation on postoperative outcomes (postoperative complications, hospital length of stay, pain at postoperative day 1) in patients undergoing elective surgery.

Methods: The authors performed a systematic review and meta-analysis of RCTs published between January 2006 and June 2023 comparing prehabilitation programmes lasting ≥14 days to 'standard of care' (SOC) and reporting postoperative complications according to the Clavien–Dindo classification. Database searches were conducted in PubMed, CINAHL, EMBASE, PsycINFO. The primary outcome examined was the effect of uni- or multimodal prehabilitation on 30-day complications. Secondary outcomes were length of ICU and hospital stay (LOS) and reported pain scores.

Results: Twenty-five studies (including 2090 patients randomized in a 1:1 ratio) met the inclusion criteria. Average methodological study quality was moderate. There was no difference between prehabilitation and SOC groups in regard to occurrence of postoperative complications (OR = 1.02, 95% c.i. 0.93 to 1.13; $P = 0.10$; $I^2 = 34\%$), total hospital LOS (–0.13 days; 95% c.i. –0.56 to 0.28; $P = 0.53$; $I^2 = 21\%$) or reported postoperative pain. The ICU LOS was significantly shorter in the prehabilitation group (–0.57 days; 95% c.i. –1.10 to –0.04; $P = 0.03$; $I^2 = 46\%$). Separate comparison of uni- and multimodal prehabilitation showed no difference for either intervention.

Conclusion: Prehabilitation reduces ICU LOS compared with SOC in elective surgery patients but has no effect on overall complication rates or total LOS, regardless of modality. Prehabilitation programs need standardization and specific targeting of those patients most likely to benefit.

Introduction

Postoperative complications occur after up to 43.5% of elective surgical procedures[1,2], resulting in prolonged hospitalization, delayed functional recovery[3] and worse oncological prognosis[4]. In addition to the negative impact on patients, postoperative complications represent a significant financial burden for healthcare systems[5], with an estimated additional cost of more than $145 billion for the USA alone[6,7]. This financial burden varies according to the severity of the complications[8] and the additional length of hospital stay (LOS).

Considerable progress has been made over the past 20 years to reduce the rate of postoperative complications due to the development of rehabilitation care pathways, such as ERAS® (Enhanced Recovery After Surgery)[9]. While patient care initially focused on the postoperative period to improve patients' outcome, clinical teams proposed to focus on preoperative care as well to improve patients' resilience to surgical stress[10–12]. This preoperative management, named 'prehabilitation', was initiated in 2005.

The prehabilitation concept traditionally encompasses interventions such as nutritional support and physical therapy (PT)[13–15]. In addition, there is increasing evidence to suggest that other types of prehabilitation interventions may be beneficial, such as behavioural[16] or cognitive training[17]. While prehabilitation programmes were first implemented 20 years ago as a unimodal approach (mainly with physical exercise[18]), prehabilitation groups and experts have increasingly promoted multimodal prehabilitation programmes, targeting at least

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physical exercise, nutrition and anxiety[13,19,20]. However, results from recent meta-analyses based on trials run between 1966 and 2018 are divergent regarding the effectiveness of prehabilitation on postoperative outcomes, particularly on LOS[21–26] and postoperative complications[27]. These meta-analyses or systematic reviews suffer from several biases: they either focused on specific surgical areas/disciplines or on particular modalities (uni- or multimodal prehabilitation separately). In addition, several recent studies of interest on the effectiveness of prehabilitation have since been published[17,28,29]. A recent umbrella review suggests that prehabilitation may improve postoperative outcomes but suffers from several limitations[25]: 78% of the included reviews focused on unimodal prehabilitation and 25% included programmes with unreported duration or shorter than 2 weeks. Due to these divergent results on prehabilitation efficacy, there is currently no gold standard for prehabilitation as its modality, content and duration are not well-defined and vary widely across studies. The existing variability across studies and over time highlights the need for meta-analysis to understand the effects of various prehabilitation modalities on patient outcomes after surgery.

The main objective of this work is to evaluate the efficacy of either uni- or multimodal prehabilitation interventions compared to the 'standard of care' (SOC) in patients undergoing elective surgeries to prevent 30-day postoperative complications, measured using the Clavien–Dindo classification. Secondary objectives were to evaluate the influence of prehabilitation interventions on hospital and ICU LOS and on postoperative pain intensity. The impact of uni- or multimodal prehabilitation interventions on these outcomes was furthermore explored in subgroup analyses.

Methods

Protocol publication

This systematic review was conducted in accordance with the methods of the Cochrane Collaboration[30], reported according to the PRISMA list[31] and to the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guidelines[32]. It was also registered in PROSPERO (International Prospective Register of Systematic Reviews, CRD42021236385).

Eligibility criteria

We included all RCTs published in English that investigated the effectiveness of uni- and multimodal prehabilitation programmes longer than 14 days before surgery compared with preoperative SOC on occurrence of postoperative complications according to the Clavien–Dindo classification up to 30 days after surgery, and/or hospital and ICU LOS, and/or pain at postoperative day one measured by the visual analogue scale (VAS) as primary or secondary outcomes. All types of elective surgical procedures were included. Studies involving paediatric patients (<18 years old) or with <20 patients were excluded.

Outcome measures

The primary outcome was the incidence of 30-day postoperative complications measured by the Clavien–Dindo classification (*Table S1*)[33]. Secondary outcomes were hospital and ICU LOS, measured in days, and postoperative pain measured by the VAS on the first postoperative day (D1).

Search strategy

The search strategy focused on data published in English between 1 January 2006 (corresponding to the beginning of the prehabilitation concept) and 13 June 2023 in the following databases: PubMed, CINAHL, EMBASE and PsycINFO. A preliminary keyword search was performed in PubMed. A second search was performed using medical subject headings (MeSH) terms. After ensuring that the equation using a combination of MeSH terms and Text Words yielded the most relevant studies, two researchers entered this equation into the four databases on 13 June 2023. The detailed equation of the MeSH terms is available online.

Study selection process

Article selection was performed using COVIDENCE systematic review software (Veritas Health Innovation, Melbourne Australia)[34]. The two lead authors (B.C. and A.C.) independently reviewed and selected studies for inclusion based on titles, abstracts and keywords (generated by the search strategy) to determine eligibility in terms of prehabilitation interventions, participants and protocols. Any disagreements were discussed until a consensus was found. If no consensus was found, a third reviewer (F.V.) determined the inclusion or exclusion of the articles in question. The two main authors retrieved the full texts of all relevant trials.

Next, inclusion or exclusion at the full-text review stage was performed independently for all articles by B.C. and A.C. and included information about participants, prehabilitation interventions, content of SOC and outcome measures that were not discussed in the abstracts. As with the first analysis, the included studies were compared, discussed, and, if no consensus was reached, assessed by the third reviewer (F.V.).

Data extraction and risk of methodological biases

Data from each article were extracted independently by B.C. and A.C. and reviewed blindly by F.V. These data included study characteristics, population characteristics, intervention details, methods and outcomes. The methodological quality of the studies was measured by the Joanna Briggs Institute RCT Critical Appraisal Tool[35]. This assessment list included 13 quality criteria that could be classified as high, moderate or low risk. The quality score for each study was determined according to the following thresholds: low risk of bias if at least 70% of responses were low risk; moderate risk if low risk responses were between 50% and 69%; and high risk of bias if less than 50% of responses were low risk[36,37].

Missing data management

If the full-text article was not found or if data were missing from the studies, the corresponding authors were contacted by email. In particular, when the LOS was not reported in median and i.q.r., the corresponding authors were contacted to obtain these measures or the respective raw data for the authors' calculation. If the corresponding authors did not respond after three emails over a 3-month period, data were considered missing. Similarly, if authors could not provide full text, articles were excluded from the analysis.

Statistics

Postoperative complications were defined as the occurrence of a complication with a grade ≥1 according to the Clavien–Dindo classification[33] (*Table S1*). LOS (total or ICU) was treated as a discrete ordinal variable ranging from 0 to X days and reported in one-day increments. Pain was measured by VAS and treated

as a discrete ordinal variable ranging from 0 to 10 and reported with one-point increments. The distribution of numerical variables was reported with the median and i.q.r., when available.

OR and median from random effect models with 95% c.i.s were calculated and included all studies with available data represented by forest plots using R software version 3.6.1 (2019–07–05) with the meta (v 4.19-0) and metamedian (v 0.1.5) libraries[38]. Heterogeneity was assessed using the χ^2 test and the I^2 statistic. Tests were considered statistically significant if $P<0.05$. An additional subgroup analysis according to separate uni- or multimodal prehabilitation had been planned in the protocol to meet the objectives of the review. For every subgroup analysis, we performed similar random-effect models analysis.

To analyse the occurrence of complications, a random-effect OR comparison approach with 95% c.i. was performed. For LOS, a common approach was used to compare differences in medians with random effect. This meant restricting the analysis to items for which median and i.q.r. were available. Medians were not inferred from means as we decided to have a rigorous approach in data integration.

Results

Research strategy

The selection process is summarized in the PRISMA 2020 flow diagram (*Fig. 1*)[39]. A total of 938 RCTs were identified and, after excluding duplicates and ineligibles, 25 RCTs were included in the meta-analysis and systematic review.

Missing data

Eighteen corresponding authors were contacted to retrieve missing data[15,40–58], of which five supplied the relevant information[40,43,52,55,56].

Study characteristics

Study characteristics are summarized in *Table 1*. Among the 25 studies included in the present review, 17 took place in Europe[41,43,47–49,51,55,56,59–66] (1250 patients), four in Canada[40,54,67,68] (263 patients), three in Australia[44,50,69] (504 patients) and one in China[70] (73 patients). The sample size ranged from 21 to 432 patients. Two studies were multicentre RCTs[44,54] (532 patients), all others were monocentric. Most studies were coordinated in university hospitals, only four were led from regional hospitals[50,52,59,60] (225 patients). None of the authors reported a conflict of interest. Manuscripts were published between 2010 and 2022.

Population

Population characteristics are summarized in *Table 1*. Thirteen studies only included patients undergoing oncological operations (785 patients), four studies included patients both with and without cancer (849 patients) and eight studies included patients undergoing non-cancer-related surgery (457 patients). Patients' co-morbidities are detailed in *Table S2*. The repartition of surgical procedures in the 25 studies was as follows: abdominal (11/24, 639 patients), thoracic (3/24, 277 patients), urologic (4/24, 272 patients), vascular (2/24, 177 patients) and orthopaedic (2/24, 51 patients). Three studies included different types of surgery (654 patients)[44,61,64]. The case mix was as follows: abdominal and urologic (432 patients), neurosurgery and abdominal (96 patients), urologic, abdominal, gynaecological and orthopaedic (126 patients).

Prehabilitation intervention and standard of care

The characteristics of prehabilitation interventions are summarized in *Table 1*. Programmes were mostly unimodal ($n=17$ studies, 1198 patients), delivered in a healthcare facility and supervised by healthcare professionals ($n=14$ studies, 1168 patients). The median duration of these prehabilitation programmes was 31.5 preoperative days (i.q.r. 27.5–41, 1984 patients). Each of the studies compared their prehabilitation programme to various SOCs according to local practice: patients were invited to either continue the routine they followed prior to surgery (11 studies, 861 patients)[41,47,49,50,55,56,59,61,67,68,70] or they received instructions for unsupervised physical exercise and nutritional advice (13 studies, 1066 patients)[40,43,44,48,51,52,54,60,63–66,69]. Most studies evaluated the impact of PT alone[40,41,43,48,51,52,54,59,60,62,65,66] (12 studies, 843 patients) or combined with nutrition or inspiratory muscle training[44,63,67–69] (5 studies, 575 patients). Exercise modalities were either endurance training (9 studies, 386 patients) or high-intensity interval training (HIIT; 4 studies, 262 patients), or a mix of both (2 studies, 164 patients). Exercise modalities were not precisely described in four studies (663 patients).

The second most studied intervention was nutrition alone[47,49,50,61] (4 studies, 259 patients) or combined with other modalities[63,67,68] (3 studies, 647 patients). Details on prehabilitation interventions and SOC are presented in *Table 2*. When available, information on patients' adherence to the protocol was collected (*Table 1*). The mean study recruitment rate was 58%, the mean adherence to the programmes was 78% and the mean attrition rate was 12%. No serious adverse event related to prehabilitation was reported.

Quality of evidence

Data on quality of evidence are presented in *Fig. 2*. The mean score for overall quality of evidence was 45%, ranging from 0% to 89%. Two studies were at low risk of bias (score >70%, 476 patients)[44,49] and 13 studies were at high risk of bias (score <50%, 627 patients)[40,43,47,50–52,54,55,61,64,65,67,68], with 10 studies of moderate quality of evidence (score ≥50% and ≤70%, 755 patients)[41,48,56,59,60,62,63,66,69,70]. The funnel plot for the primary outcome is symmetrical, and more than 95% of the included studies are within the fixed-effect summary estimate, thereby not providing any evidence of publication bias, as shown in *Fig. 3*.

Primary outcome of included studies

Only one study reported postoperative complications at postoperative day 30 as a primary outcome according to the Clavien–Dindo classification (57 patients)[43]. Six studies focused on postoperative complications without using the Clavien–Dindo classification as the primary outcome (937 patients)[43,44,49,59,62,66]. Eight studies used feasibility and acceptability of the prehabilitation programme as primary outcomes (352 patients)[41,50–52,54,60,63,69]. The focus of seven studies was mainly on prehabilitation's influence on patients' perioperative functional capacity (497 patients)[40,48,55,56,67,68,70]. One study measured postoperative pain without using the VAS[64]. None of the studies had LOS as a primary outcome.

Primary outcome: postoperative complications at postoperative day 30 according to the Clavien–Dindo classification

Fifteen studies collected data on postoperative complications according to the Clavien–Dindo classification at day 30[41,43,47–51,54,56,63,66–70], allowing for analysis of 852 patients

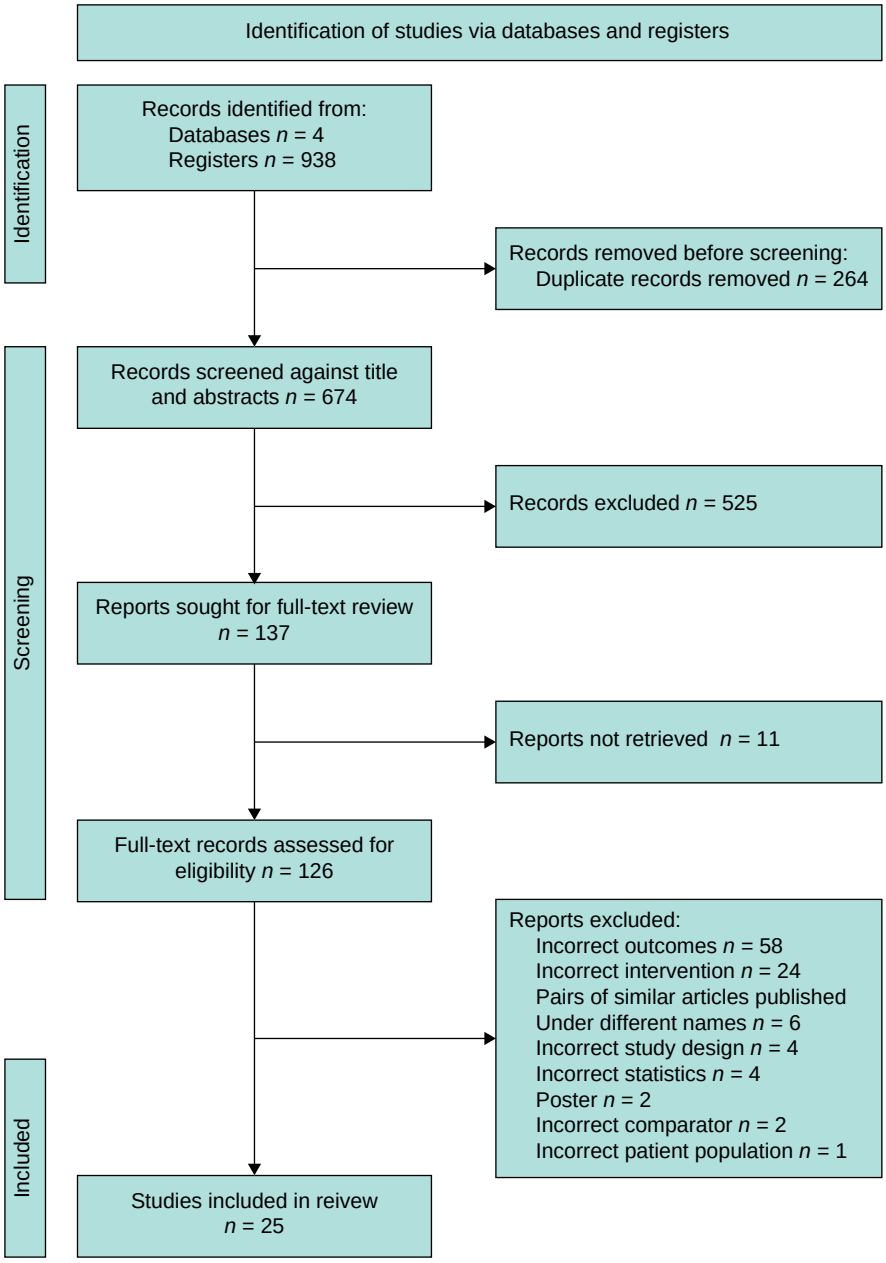


Fig. 1 PRISMA flow chart

(*Fig. 4*). The procedures were mostly abdominal (11 studies, $n = 588$), followed by urologic (3 studies, $n = 195$) and thoracic (1 study, $n = 73$). Of these 14 studies, one found a significant reduction of postoperative complications in the prehabilitation group, all others showed no effect. Overall, no statistical difference was observed between the prehabilitation and SOC cohorts (OR = 1.02, 95% c.i. 0.93 to 1.13; $P = 0.10$; $I^2 = 34\%$, random effect, *Fig. 4*).

Secondary outcomes

Total length of hospital stay

Twenty-two studies (1770 patients) measured the efficacy of prehabilitation on the total LOS[40,41,43,44,47–49,51,52,55,56,59–65,67–70], with 1672 patients analysed. Most of these studies were in patients undergoing abdominal surgery (9 studies, 435 patients), followed by thoracic (3 studies, 246 patients), urologic (3 studies, 151 patients) and vascular (2 studies, 172 patients) surgery. Three studies included a combination of general, urologic, gynaecologic and orthopaedic surgeries representing 619 patients. Of those 22 studies, two found a reduction in the total LOS; however, overall, no statistical difference was observed between the prehabilitation and the SOC groups (median differences (MD) = –0.13 days; 95% c.i. –0.56 to 0.28; $P = 0.53$; $I^2 = 21\%$, *Fig. 5a*).

Length of stay in the ICU

Five studies measured the median LOS in the ICU[41,48,49,59,69] with a total of 278 patients analysed. Of these five studies, one found a significant reduction in the ICU LOS. Procedures were mostly abdominal (three studies, 114 patients). A statistical difference was observed in favour of prehabilitation compared with the SOC groups ($n = 278$, MD = –0.57 days; 95% c.i. –1.10 to –0.04; P

Table 1 Study characteristics

Author and year	Sample size (total)	Age prehab. (years)	Age SOC (years)	Surgery	Surgical indication	Prehab. modality	Prehab. duration	Measured outcome	Adherence (%)
Au *et al.*[40]	42	61.4(7.8)	58.4(6.1)	Prostatectomy	Cancer	PT	5	LOS	81.5
Barnejee *et al.*[41]	60	71.6(6.8)	72.5(8.4)	Cystectomy	Cancer	PT	3–6	CD, LOS	NR
Barakat *et al.*[51]	124	73.8(6.5)	72.9(7.9)	AAA repair	AAA	PT	6	LOS	NR
Berkel *et al.*[43]	57	74(7)	73(6)	Colorectal	Cancer	PT	2–4	CD, LOS	90
Boden *et al.*[44]	432	65 (52–72)	67.5 (56–75)	Major abdominal surgery	Multiple	PT, IMT	6	LOS	94
Chakravartty *et al.*[47]	28	44 (26–60)	39 (24–66)	RYGB	Obesity	Nutrition	4	CD, LOS	NR
Dunne *et al.*[48]	37	61 (56–66)	62 (53–72)	Hepatobiliary	Cancer	PT	4	CD, LOS	94
Fulop *et al.*[56]	184	70 (60–75)	70 (64–75)	Colorectal	Cancer	PT, IMT, Nutrition, Cognition	3–6	CD, LOS	NR
Gloor *et al.*[66]	106	66 (24–90)	65 (29–86)	Colorectal	Multiple	PT	3–6	CD	NR
Grąt *et al.*[49]	55	52 (47–58)	50 (35–61)	Liver transplant	Cirrhosis	Nutrition	>2	CD, LOS	92.3
Hollis *et al.*[50]	50	48.2(13.3)	51.8(12.2)	General surgery	Multiple	Nutrition	8	CD, LOS	93
Hoogeboom *et al.*[60]	21	77(3)	75(5)	Hip replacement	Arthrosis	PT	3–6	LOS	91
IJmker-Hemink *et al.*[61]	126	63.3(12)	62.3(12.7)	Digestive, gynaecologic, orthopaedic, urologic	Multiple	Nutrition	3	LOS	35
Karenovics *et al.*[62]	164	64(13)	64(10)	Thoracic	Cancer	PT	>4	LOS	87
Karlsson *et al.*[63]	21	84 (76–85)	74 (73–76)	Prostatectomy	Cancer	PT, IMT, Nutrition	2	CD, LOS	97
Liu *et al.*[70]	73	56.2(10.3)	56.2(8.7)	AAA repair	AAA	PT, Nutrition, Cognition	2	CD, LOS	NR
Minnella *et al.*[67]	51	67.3(7.4)	68.0(11.6)	Colorectal	Cancer	PT, Nutrition	5	CD, LOS	63
Minnella *et al.*[68]	70	69.7(10.2)	66.0(10.2)	Major abdominal surgery, urologic	Multiple	PT, Nutrition, Cognition	4	CD, LOS	83.3
Moug *et al.*[51]	48	65.2(11.4)	66.5(9.6)	Knee replacement	Arthrosis	PT	14	CD, LOS	75
Oosting *et al.*[52]	30	76.9(6.3)	75.0(6.3)	RYGB	Obesity	PT	5	LOS	NR
Rolving *et al.*[64]	96	51.4(9.2)	47.7(8.9)	Hepatobiliary	Cancer	Cognition	6	LOS	24
Santa Mina *et al.*[54]	100	61.2(8)	62.2(6.9)	Colorectal	Cancer	PT	6.5	CD, LOS	69.2
Sebio García *et al.*[55]	40	70.9(6.1)	69.4(9.4)	Liver transplant	Cirrhosis	PT, IMT	7.5	LOS	NR
Steffens *et al.*[69]	22	66 (46–70)	62 (48–72)	General surgery	Multiple	PT, IMT	2–6	CD, LOS	93
Tew *et al.*[65]	53	74.6(5.5)	74.9(6.4)	Hip replacement	Arthrosis	PT	5	LOS	75.8

Age is expressed as mean(s.d.) or median (interquartile range (i.q.r.)), prehabilitation duration is expressed in weeks. Prehab., prehabilitation group; SOC, 'standard of care'; AAA, abdominal aortic aneurysm; CD, Clavien–Dindo classification; IMT, inspiratory muscle training; LOS, length of stay; NR, not reported; PT, physical therapy; RYGB, Roux-en-Y gastric bypass.

= 0.03; I^2 = 46%, *Fig. 5b*). The ICU LOS was reduced by 28% in the prehabilitation compared to the SOC group.

Pain

None of the included studies measured pain with a VAS at postoperative D1. Among studies having a pain outcome, pain was not assessed using the specific method defined in the present study setup. Instead, pain was measured using other scales or was assessed at different time points, typically in the long term (postoperative months 3–6).

Subgroup analysis

No statistically significant difference in the effectiveness of prehabilitation according to the different prehabilitation modalities was found, either on postoperative complications for both unimodal prehabilitation (n = 478, RR 0.92, 95% c.i. 0.70 to 1.20; P = 0.10; I^2 = 40%, random-effect model; *Fig. S1*) or multimodal prehabilitation (n = 374, RR 1.09, 95% c.i. 0.82 to 1.44; P = 0. 02; I^2 = 63%, random-effect model; *Fig. S2*), or on total LOS for both unimodal (n = 371, MD = −0.14 days; 95% c.i. −0.69 to 0.42; P = 0.63; I^2 = 43%; *Fig. S3*) and multimodal prehabilitation (n = 392, MD = −0.11 days; 95% c.i. −0.74 to 0.51; P = 0.63; I^2 = 43%; *Fig. S4*). There was also no difference in the abdominal surgery group on postoperative complication rate (579 patients, RR = 1.03, 95% c.i. 0.83 to 1.26; P = 0.11; I^2 = 36%; *Fig. S5*) or LOS (n = 435, MD = −0.25, 95% c.i. −0.86 to 0.36; P = 0.42; I^2 = 1.55%; *Fig. S6*) or in the other surgery types group (n = 273, RR = 1.00, 95% c.i. 0.95 to 1.05; P = 0.31; I^2 = 16%, random-effect model; n = 1237, MD = −0.06 days, 95% c.i. −0.60 to 0.48; P = 0.83; I^2 = 40%; for postoperative complication and LOS, respectively; *Fig. S7, S8*, respectively).

Discussion

In this meta-analysis, which examined RCTs with prehabilitation programmes longer than 14 days and compared them to SOC for

Table 2 Prehabilitation modalities

Author and year	Prehabilitation intervention	Standard of care
Au *et al.*[40]	Home-based moderate intensity aerobic and resistance exercises prescribed and demonstrated shortly after consenting to surgery. Manual detailing exercise prescription with supporting behaviour change strategies.	Book on maintaining a healthy lifestyle after a prostate cancer diagnosis with no further exercise support.
Barnejee *et al.*[41]	Two supervised training sessions per week in an exercise facility for 6 weeks. Fractionated high-intensity aerobic exercise (cycle ergometer).	Patients in the control group were advised to carry on with their lifestyles in the 'usual way'.
Barakat *et al.*[59]	Instructions and timetable to join hospital-based exercise classes, 3 times a week, 1-hour duration, during the 6 preoperative weeks.	Continued with their normal lifestyle, and avoid any additional, unsupervised exercises.
Berkel *et al.*[43]	Three one-hour supervised sessions of physical therapy per week. High-intensity interval training on a cycle ergometer and resistance training.	Nutrition counselling and advice on smoking cessation.
Boden *et al.*[44]	One 30-minute session with a physiotherapist for education and prevention of PPC, breathing exercises, delivery of a booklet.	Breathing exercise booklet.
Chakravartty *et al.*[47]	800 kcal VLCD regimen for 4 weeks. VLCD contained 3 pints of semi-skimmed milk, equivalent to 1704 ml (total intake of 800 kcal, 82 g carbohydrate, 61 g protein and 30 g fat), multivitamin and mineral supplementation, plus minimum of 2 l of energy-free liquid.	Continued with their usual diet.
Dunne *et al.*[48]	12 interval exercise sessions delivered by a cycle ergometer (moderate and vigorous intensity).	Patients were encouraged to follow clinical advice on exercise before surgery.
Fulop *et al.*[56]	Information booklet, work diary, multimodal home-based exercise programme plus weekly in-hospital exercise sessions, deep breathing, incentive spirometry, nutritionist evaluation and oral nutritional supplementation, 60-minute session with a trained psychologist (techniques to reduce anxiety + lifestyle advice).	Not reported.
Gloor *et al.*[66]	Training twice a week with a qualified physiotherapist, and once supervised at home. Each session was 90 min (10 min warm up, 35 min endurance training (HIT), 35 min strength training, 10 min cool down).	Continued with usual physical activities
Grat *et al.*[49]	Probiotic capsules once/day until transplant (*Lactococcus lactis* PB411 (50.0%), *Lactobacillus casei* PB121 (25.0%), *Lactobacillus acidophilus* PB111 (12.5%) and *Bifidobacterium bifidum* PB211 (12.5%)).	Daily placebo.
Hollis *et al.*[50]	VLCD programme (+ 2 cups vegetable salad, 2 l non-energy-free fluids, one teaspoon of vegetable oil).	Not reported.
Hoogeboom *et al.*[60]	60 min of supervised exercise sessions at the outpatient clinic twice a week for 3–6 weeks preoperatively. Patients were encouraged to exercise at home.	One group-based education session (early mobilization, surgery and anaesthesia, restricted movements, benefits of activity).
IJmker-Hemink *et al.*[61]	Pre-cooked meals for 3 weeks: 6 protein-rich dishes per day (morning shake, 2 lunch dishes, snack, dinner and dessert for each day (avg energy 1553 kcal/day, avg protein 60.8 g/day)) + information leaflet describing personal protein requirements (1.2 g/kg body weight) and 'protein-meter' for protein intake.	Usual care with habitual diet followed.
Karenovics *et al.*[62]	Up to 3 weekly supervised high-intensity training sessions using a cycle ergometer. Advice on active mobilization and risk factor management.	Not reported.
Karlsson *et al.*[63]	2–3 supervised sessions per week for 6 weeks. Inspiratory muscle training (30 breaths twice a day), high-intensity functional strength exercises. Difficulty was increased for progression. + Usual care	Ordinary preoperative information and recommendation of 150 min per week of moderate physical intensity.
Liu *et al.*[70]	Aerobic and resistance exercises, respiratory training, nutritional counselling with whey protein supplementation, psychological adjustments (basic mental relaxation skills), conventional guidance.	Not reported.
Minnella *et al.*[67]	Home-based programme (aerobic exercise and moderate continuous training 3 days per week after one demonstration session with a kinesiologist). Dietary advice + whey protein supplement (daily protein intake of 1.2 to 1.5 g/kg).	No specific intervention before surgery.
Minnella *et al.*[68]	Same as Minnella 2018 + relaxation and imaging techniques.	No specific intervention before surgery.
Moug *et al.*[51]	8 weeks of graduated goals calculated from the baseline stepping count. Walking diary and use of a pedometer. Follow-up telephone calls. Support person (for example, spouse) to assist in their adherence to the programme.	Maintain their normal level of physical activity.

(continued)

Table 2 (continued)

Author and year	Prehabilitation intervention	Standard of care
Oosting *et al.*[52]	Home-based exercise programme with patient-tailored functional activities and walking. Pedometer (goal = minimum 30 min per day) + 30 min supervised sessions twice a week for 3–6 weeks.	Usual care: one session of instructions, a single group session supervised by a physical therapist 3 weeks before surgery.
Rolving *et al.*[64]	Four 3-hour group sessions directed by a multidisciplinary team on interaction between cognition and pain perception, coping strategies, pacing principles, ergonomic directions, return to work, details about the surgical procedure.	Standard preoperative information.
Santa Mina *et al.*[54]	Pelvic floor muscle exercise and total body exercises. 60 min of unsupervised, home-based, moderate intensity exercise 3–4 days per week. (Exercise manual with online exercises.)	Manual detailing a pelvic floor training regimen.
Sebio Garcia *et al.*[55]	One hour supervised pulmonary prehabilitation programme 3–5 times per week. Moderate endurance (ergometer) and resistance training.	Usual care—no exercise training.
Steffens *et al.*[69]	Exercise sessions: 1 h individualized, hospital-based training session once a week for 2–6 weeks (aerobic and endurance, respiratory, muscle strength) + personalized home exercises + activity tracker (goal = 30 min walk/day).	Nutritional counselling and advice on smoking cessation, reduction of alcohol intake. Instruction to maintain normal daily activities.
Tew *et al.*[65]	Three hospital-based supervised exercise sessions on a cycle ergometer per week for the 4 consecutive weeks preceding their operation date.	Usual care, which comprised evidence-based medical optimization.

PPC, postoperative pulmonary complication; VLCD, very low-calorie diet.

any type of elective surgery over the last 15 years, no significant difference was found between groups regarding the incidence of postoperative complications or total LOS. The authors identified a significant reduction of LOS in ICUs of approximately 28% in favour of prehabilitation as compared to SOC. The effect of prehabilitation on postoperative day 1 pain scores has not been studied in any included study. All analyses showed moderate statistical heterogeneity. Subgroup analyses did not identify increased efficacy of prehabilitation depending on modality, either uni- or multimodal, with moderate to significant heterogeneity, respectively. To the authors' knowledge, this meta-analysis is the first to include studies combining several types of surgeries and different prehabilitation modalities in the same analysis. The current methodology rigorously followed the international recommendations for conducting a systematic review and meta-analysis[26,71].

These results on complication rate are contradictory to the last retrospective epidemiological data on more than 1500 patients[72] as well as to a recent observational study[73], and other meta-analyses focusing on abdominal and cardiovascular operations which showed that prehabilitation is effective on both clinical and economic outcomes[43,49]. Several explanations for this discrepancy are possible: heterogeneity in prehabilitation programmes limits statistical power, methodological bias may skew results, and target populations limit the generalizability of results.

First, programmes included in this meta-analysis were not standardized and did not always meet the guidelines issued since 2017 by the Macmillan[74] or the Franco Carli groups[75], the ERAS initiative[9] or the nutritional recommendations of the European Society for Clinical Nutrition and Metabolism (ESPEN)[76]. Many studies to date have been conducted on small patient cohorts with varied programmes and outcomes, primarily focusing on safety, starting with physical exercise which could include either strength training, or aerobic exercise or high-intensity training or a combination of those, all aiming at improving patients' functional status yet having different effects on the body. Also, despite a growing number of studies on the effectiveness of multimodal prehabilitation, a large majority of included RCTs tested only a unimodal intervention, mostly PT or nutrition[77]. Only 25% of the included studies focused on multimodal prehabilitation, inducing a probable lack of power to demonstrate the efficacy of this modality. Finally, only studies with prehabilitation programmes longer than 14 days were included. Although this has led to a selection bias and lack of power because it drastically limited the number of studies included, the criterion was chosen so we could focus on prehabilitation programmes designed for a duration compatible with a change in preoperative functional parameters[13,78]. This approach has been adopted by others[25,44,61,79] and is based on the postulate that exercise, nutrition and brain function have an impact on immune system functions[14,80,81], which are key players in surgical recovery[82,83]. In addition, exercise can increase physiological reserve and the body's ability to cope with increased metabolic demand, while nutritional intervention can help reduce sarcopenia[14]. The fact that heterogeneity remains under 34% for all outcomes, despite different programmes and surgery types, validates the authors' approach of pooling all these data together to a certain extent. Including various prehabilitation modalities and surgery types allowed for a pragmatic analysis of prehabilitation in multiple surgical disciplines, enabling a broad generalizability of the results. Additionally, subgroup analysis based on prehabilitation type (uni- or multimodal) or type of surgery did not demonstrate a preference for prehabilitation over standard of care.

When evaluating the efficacy of prehabilitation, it raises questions about the type of outcome to be studied from both the patient's and medical perspectives, aiming to provide the best patient-centred care. For instance, although postoperative delirium is a common complication among elderly patients that could potentially be mitigated by prehabilitation[17], none of the included studies reported this outcome. To better meet patients' needs, patient self-reported measures (PROM-10 or 29, for example)[84,85] have been developed and will probably provide answers to those questions in the future.

Second, the dramatic variability in methodological quality limits the interpretation and generalizability of the results. This heterogeneity is partially explained by the inconsistency in

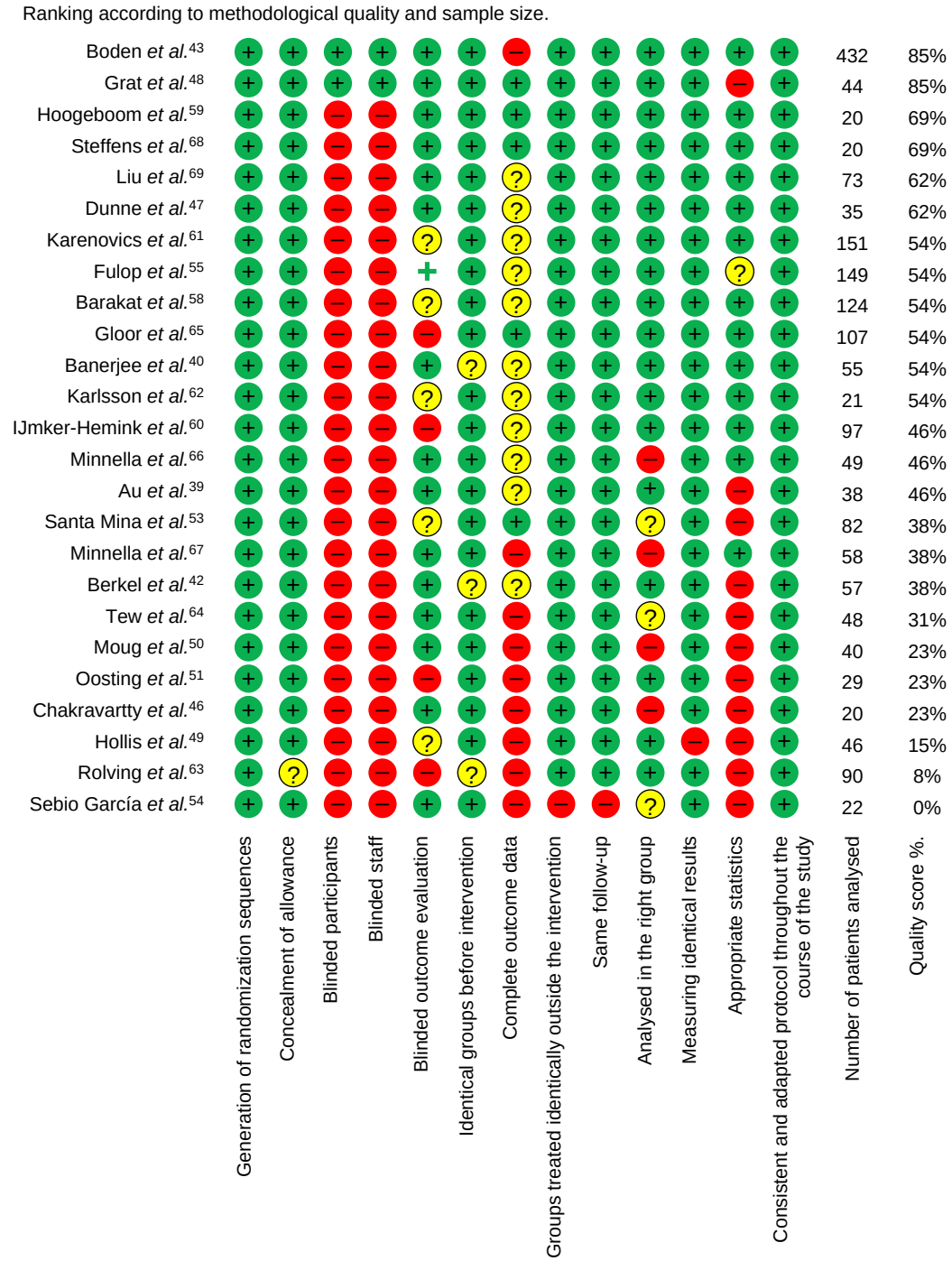


Fig. 2 Quality assessment of included studies

prehabilitation programmes as discussed above, as well as the raw methodology. Indeed, an invariable feature associated with PT prehabilitation is the impossibility of conducting these studies in a patient-blinded setting. In addition, interventions in the SOC groups overwhelmingly comprised dietary advice booklets and PT, which could be a confounding factor. Moreover, the recruitment rate in these studies was relatively low (60% on average), creating a possible selection bias. The number of studies included was also drastically decreased by the choice of the complication reporting scale (Clavien–Dindo), which also produced a selection and evaluation bias. However, this classification is the most robust classification for complication evaluation and allows for reproducible and comparable results. This effectively translated in a heterogeneity of 34% for the impact of prehabilitation on postoperative complication when other recent meta-analysis had a heterogeneity ranging from 43% to 77%[26,86]. Of note, most studies took place in a European setting, limiting the generalizability of the results to other healthcare systems and world regions. Results on postoperative complication may also be driven by the high proportion of abdominal surgery (11 of 15 studies). However, even when conducting subgroup analysis specifically focusing on non-abdominal surgeries, no efficacy of prehabilitation on postoperative complications or total hospital length of stay was observed.

While the current analysis does not show an impact of prehabilitation on total hospital LOS, prehabilitation is associated with a decrease in ICU LOS. Along with existing literature on specific high-risk patient populations[21,22,24,26,77,87,88], this provides compelling arguments for the potential benefits of prehabilitation in preoperative care for at-risk populations. It is important to note that a reduction in ICU LOS is a significant outcome in itself, contributing to improved resource utilization and potentially better patient outcomes, especially as high-dependency units are associated with a greater risk of delirium[89], mortality[90], post-traumatic stress disorder[91] and higher financial burden[92]. Although this reduction in ICU LOS could be due to a decrease in severe complications, especially in frail patients, further studies are needed to provide direct evidence for this correlation. Indeed, while preoperative frailty (broadly defined by a multidimensional state of reduced physiological reserve[93]) has been identified as a major risk factor for delayed postoperative recovery[10,11,94,95], most of the studies included in the review did not measure participants' frailty before prehabilitation and did not adapt their programmes accordingly, which may explain this lack of effect of prehabilitation in the general population. A meta-analysis targeting frail patients undergoing abdominal surgery conducted by Daniels *et al.* in 2020[24] showed that a multimodal prehabilitation significantly reduced severe complications (Clavien–Dindo ≥III).

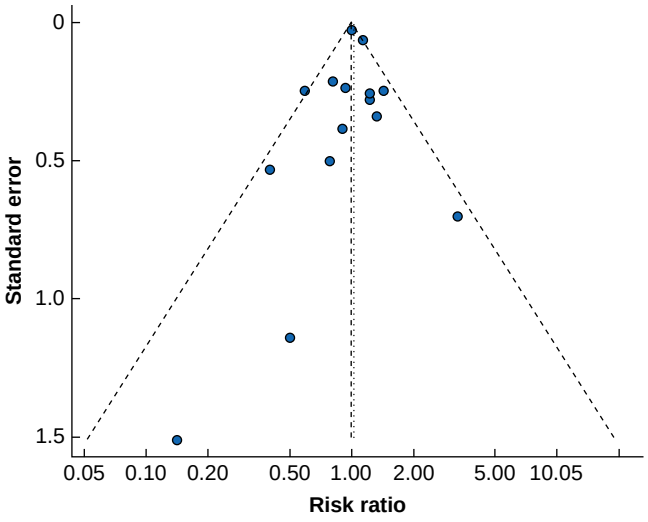


Fig. 3 Funnel plot

Patient adherence is another critical factor in the effectiveness of prehabilitation, which could potentially explain the current results. This is further highlighted by recent findings showing negative results of home-based prehabilitation for frail patients undergoing cancer surgery[96]. Adherence could be improved by integrating motivational interviews into prehabilitation programmes, by improving their accessibility (delivery of programmes via tele-coaching and real-time adaptation to patients' difficulties in changing their lifestyle), or by using connected wearable devices both to monitor and prompt patients to comply better with their prehabilitation programme.

This also highlights the necessity for performance tools to stratify patients at risk for postoperative complications and furthermore patients who would benefit from prehabilitation. Current tools to evaluate patients' frailty (such as the risk analysis index-administrative [RAI-A][97] that is to date the most performant frailty evaluation tool, or the American College of Surgeons National Surgical Quality Improvement Program [ACS NSQIP] surgical risk score, or Fried's frailty score) based solely on clinical data lack performance[98,99] and are barely used in clinical practice. Recently, new approaches integrating immune parameters, and in particular intracellular signalling, in addition to clinical data have made it possible to achieve unequalled

	Prehab.		SOC					
Study or subgroup	Events	Total	Events	Total	Risk ratio	RR	95% c.i.	Weight (%) (common)	Weight (%) (random)
Banerjee *et al.*[40]	4	30	10	30		0.40	(0.14, 1.14)	4.7	0.9
Berkel *et al.*[42]	12	28	21	29		0.59	(0.37, 0.96)	9.7	3.9
Chakravartty *et al.*[46]	1	10	2	10		0.50	(0.05, 4.67)	0.9	0.2
Dunne *et al.*[47]	8	19	7	15		0.90	(0.42, 1.92)	3.7	1.7
Fulop *et al.*[55]	17	77	12	72		1.32	(0.68, 2.58)	5.8	2.1
Gloor *et al.*[65]	52	54	45	53		1.13	(1.00, 1.29)	21.3	27.4
Grat *et al.*[48]	5	21	7	23		0.78	(0.29, 2.09)	3.1	1.0
Hollis *et al.*[49]	0	20	2	14		0.14	(0.01, 2.73)	1.4	0.1
Karlsson *et al.*[62]	6	11	2	12		3.27	(0.83, 12.95)	0.9	0.5
Liu *et al.*[69]	37	37	36	36		1.00	(0.95, 1.05)	17.4	42.5
Minnella *et al.*[66]	14	24	18	25		0.81	(0.53, 1.23)	8.3	5.1
Minnella *et al.*[67]	16	30	16	28		0.93	(0.59, 1.48)	7.8	4.2
Moug *et al.*[50]	12	18	12	22		1.22	(0.74, 2.02)	5.1	3.6
Santa Mina *et al.*[53]	18	42	14	40		1.22	(0.71, 2.12)	6.7	3.1
Steffens *et al.*[68]	10	11	7	11		1.43	(0.88, 2.32)	3.3	3.9
Common effect model		432		420		0.99	(0.89, 1.11)	100.0	–
Random effects model						1.02	(0.93, 1.13)	–	100.0
Heterogeneity: $\tau^2 = 0.0053$, $P = 0.10$, $I^2 = 34\%$									

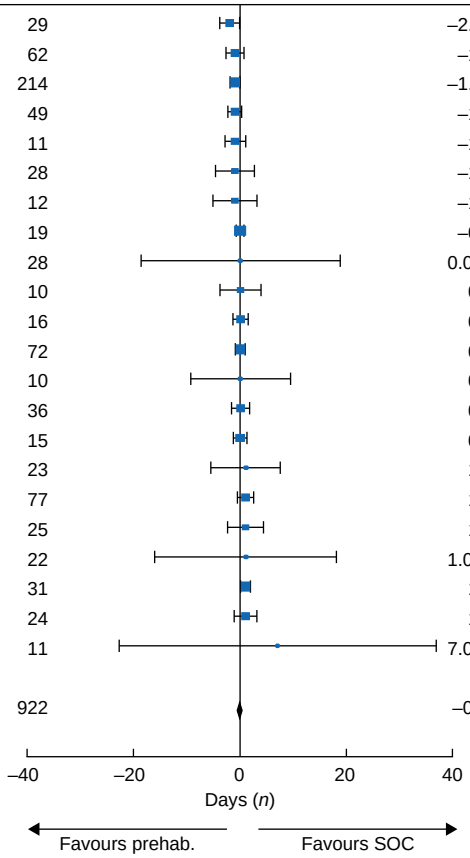
Fig. 4 Impact of prehabilitation on postoperative complications according to the Clavien–Dindo classification

Events, number of complications; prehab., prehabilitation group; SOC, standard of care group; Total, total number of patients; Weight, study weight.

a Hospital LOS

	Prehab.				SOC				Median difference	Median difference (95% c.i.)
	Median	Q1	Q3	Total (*n*)	Median	Q1	Q3	Total (*n*)		
Berkel *et al.*[42]	5	4	7.75	28	7	5	9	29		–2.00 (–3.88, –0.12)
Barakat *et al.*[58]	7	5	9	62	8	6	12.3	62		–1.00 (–2.72, 0.72)
Boden *et al.*[43]	8	6	11	218	9	7	13	214		–1.00 (–1.96, –0.04)
IJmker-Hemink *et al.*[60]	2	2	6	48	3	2	5	49		–1.00 (–2.33, 0.33)
Karlsson *et al.*[62]	5	4	6	10	6	4	7	11		–1.00 (–3.01, 1.01)
Minnella *et al.*[67]	9	7	15	30	10	7.5	14.5	28		–1.00 (–4.60, 2.60)
Sebio García *et al.*[54]	2	1.25	10	10	3	2	4.25	12		–1.00 (–5.07, 3.07)
Au *et al.*[39]	1.7	1	1.92	19	1.74	1	2	19		–0.04 (–0.61, 0.53)
Banerjee *et al.*[40]	7	4	78	27	7	5	107	28		0.00 (–18.63, 18.63)
Chakravartty *et al.*[46]	3	2	3	10	3	2	9	10		0.00 (–3.81, 3.81)
Dunne *et al.*[47]	5	4	6	19	5	4.5	7	16		0.00 (–1.44, 1.44)
Fulop *et al.*[55]	8	7	10	77	8	7	9	72		0.00 (–0.76, 0.76)
Hoogeboom *et al.*[59]	6	5	22	10	6	4	7	10		0.00 (–9.35, 9.35)
Liu *et al.*[69]	8	6	10	37	8	7	11	36		0.00 (–1.72, 1.72)
Oosting *et al.*[51]	5	4.5	5.5	14	5	4	6.5	15		0.00 (–1.27, 1.27)
Grat *et al.*[48]	18	16	23	21	17	14	29	23		1.00 (–5.48, 7.48)
Karenovics *et al.*[61]	10	8	12	74	9	7	13	77		1.00 (–0.51, 2.51)
Minnella *et al.*[66]	8	5.75	11.75	24	7	5.5	12.5	25		1.00 (–2.40, 4.40)
Moug *et al.*[50]	11	6	37	18	10	0	38.2	22		1.00 (–16.07, 18.07)
Rolving *et al.*[63]	5	4	6	59	4	4	6	31		1.00 (–0.16, 1.84)
Tew *et al.*[64]	7	4.5	8.5	24	6	4	8	24		1.00 (–1.10, 3.10)
Steffens *et al.*[68]	36	15	52	9	29	15	53	11		7.00 (–22.71, 36.71)
Total (random effect)				848				922		–0.13 (–0.56, 0.29)

Median difference –0.13, 95% c.i. (–0.56, 0.28), $P = 0.53$, $I^2 = 21\%$



b Critical care LOS

	Prehab.				SOC				Median difference	Median difference (95% c.i.)
	Median	Q1	Q3	Total (*n*)	Median	Q1	Q3	Total (*n*)		
Barakat *et al.*[58]	1	1	2	62	2	1	2	62		–1.00 (–1.34, –0.66)
Dunne *et al.*[47]	1	1	2	19	1.5	1	2	16		–0.50 (–1.14, 0.14)
Banerjee *et al.*[40]	1	1	10	27	1	1	7	28		0.00 (–2.33, 2.33)
Grat *et al.*[48]	4	4	5	21	4	3	5	23		0.00 (–0.86, 0.86)
Steffens *et al.*[68]	6	4	7.5	9	6	3.8	9.5	11		0.00 (–3.70, 3.70)
Total (random effect)				138				140		–0.57 (–1.10, –0.04)

Median difference –0.157, 95% c.i. (–1.10, –0.04), $P = 0.03$, $I^2 = 46\%$

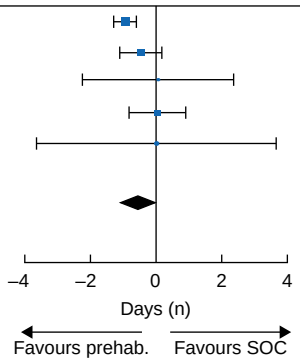


Fig. 5 (a) Impact of prehabilitation on total hospital length of stay and (b) Impact of prehabilitation on critical care unit length of stay

LOS, length of stay; prehab., prehabilitation group; Q1, first quartile (25%); Q3, third quartile (75%); SOC, standard of care group; Total, total number of patients.

predictive performance for postoperative infections (AUC 0.94 *versus* 0.63 when limited to clinical data using the ACS NSQIP surgical risk score[100]).

Considering the numerous challenges associated with prehabilitation, such as accurately identifying patients at risk for postoperative complications and determining who would benefit from prehabilitation, as well as ensuring sufficient adherence (which often requires effective coordination between healthcare workers, patients and caregivers) to ensure the programme is correctly followed and yields timely and effective results in an appropriate setting, it may be worth considering that a well-implemented unimodal programme could be sufficient. This is especially relevant because the current results did not demonstrate superior efficacy of multimodal compared to unimodal prehabilitation. Such a unimodal programme would still address patients' needs by involving them as major participants in their care and recovery[19].

In conclusion, this meta-analysis demonstrates positive and original results concerning the effect of prehabilitation programmes longer than 14 days on the reduction of ICU LOS. No effect on complications or hospital LOS criteria was found. In accordance with the Cochrane recommendations, an analysis of the effect on postoperative pain was not feasible according to the predefined criteria (that is, VAS at postoperative day one). These data suggest the importance of standardizing (both in prehabilitation modality and actual action within each modality) and evaluating prehabilitation programmes and improving the definition of patients most likely to benefit from them (that is, at-risk patients undergoing elective surgery). However, there was significant heterogeneity among the included studies, both in terms of methodology and populations targeted, which may limit the generalizability of the current findings. Additionally, this meta-analysis does not provide any insight into the long-term effects of prehabilitation on quality of life or functional outcomes.

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Author contributions

Amélie Cambriel (Conceptualization, Methodology, Writing—original draft, Writing—review & editing), Benjamin Choisy (Conceptualization, Formal analysis, Methodology, Writing—original draft, Writing—review & editing), Julien Hedou (Formal analysis), Marie Pierre Bonnet (Conceptualization, Methodology, Writing—review & editing), Jeremie LeFevre (Writing—review & editing), Souad Fellous (Formal analysis), Thibault Voron (Writing—review & editing), Dyani Gaudilliere (Writing—original draft, Writing—review & editing), Cindy Kin (Writing—review & editing), Brice Gaudilliere (Conceptualization, Methodology, Supervision, Writing—review & editing), and Franck Verdonk (Conceptualization, Methodology, Supervision, Writing—original draft, Writing—review & editing)

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

Full data are available upon request to the corresponding author.

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