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A systematic review and meta-analysis of high-quality randomized controlled trials on the role of prehabilitation programs in colorectal surgery

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ABSTRACT

Background: Prehabilitation is gaining popularity in colorectal surgery but lacks high-quality postoperative outcomes data. This meta-analysis explored whether prehabilitation impacts postoperative outcomes.

Methods: In this meta-analysis, compliant with Preferred Reporting Items for Systematic reviews and Meta-Analyses, we searched PubMed and Scopus through November 2022. High-quality randomized control trials involving adults who underwent colorectal surgery with/without exercise-based prehabilitation were included. The main outcomes were short-term postoperative morbidity, readmissions, and length of stay. Random-effect meta-analyses were performed, and statistical heterogeneity was assessed using the I^2 statistic.

Results: Seven high-quality randomized control trials comprising 1,225 patients were included. The median prehabilitation duration was 4 (2–4) weeks. Four studies compared prehabilitation and standard of care, and 3 compared prehabilitation and rehabilitation. Exercise-based prehabilitation did not reduce the odds of short-term complications (odds ratio 0.62, 95% confidence interval 0.27–1.40, $P = .25$, $I^2 = 68\%$) or readmission (odds ratio 1, 95% confidence interval 0.73–1.46, $P = .85$, $I^2 = 0\%$). The prehabilitation group had shorter length of hospital stay (weighted mean difference -0.2 , 95% confidence interval -0.25 to -0.14 , $P < .0001$, $I^2 = 43.3\%$). Prehabilitation and rehabilitation had similar odds of short-term complications (odds ratio 1.03, 95% confidence interval 0.56–1.89, $P = .91$, $I^2 = 33\%$), length of stay (weighted mean difference -0.16 , 95% confidence interval -0.47 to 0.16 , $P = .33$, $I^2 = 59\%$), and readmission (odds ratio 1.25, 95% confidence interval 0.28–5.56, $P = .77$, $I^2 = 52\%$). The only benefit of prehabilitation over rehabilitation was better 6-minute walking distance test results at time of surgery (weighted mean difference: -9.4 m; 95% confidence interval -18.04 to 0.79 , $P = .03$, $I^2 = 42\%$).

Conclusion: Prehabilitation provided decreased postoperative length of hospital stay and improved preoperative functional outcomes, but not reduced odds of complications and/or readmissions. Prehabilitation and rehabilitation had similar clinical outcomes.

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Introduction

Prehabilitation is defined as “a process on the continuum of care that occurs between the time of diagnosis and the beginning of acute treatment, includes physical and psychological assessments that establish a baseline functional level, identifies impairments, and provides targeted interventions that improve a patient’s health

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to reduce the incidence and the severity of current and future impairments.”¹ The fourth version of the Enhanced Recovery After Surgery (ERAS) guidelines,² among others, highlighted the lack of high-quality evidence on the effect of prehabilitation in patients undergoing colorectal surgery and recommended further research in order to consider whether prehabilitation should be a mandatory element of the ERAS protocol.

Recent meta-analyses^{3–7} failed to add high-quality evidence to the current literature, as they either included nonrandomized trials or trials in which patients underwent “abdominal” surgery in general and not colorectal in particular. Another well-conducted meta-analysis⁸ of randomized controlled trials (RCTs) included RCTs that compared exercise-based prehabilitation with rehabilitation programs that entailed the same type of exercise. Therefore, definitive conclusions on the benefit of prehabilitation cannot be drawn. More RCTs^{9–11} were recently published on this matter. Therefore, the objective of this study was to provide high-quality evidence on the effect of prehabilitation programs on postoperative clinical outcomes to possibly shed light on this gray area of the ERAS guidelines.

Methods

Review registration

This systematic review was prospectively registered in PROSPERO (CRD42022357032) and has been reported in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 statement.¹² Given the nature of the study that does not involve patient contact or intervention, approval from our institutional review board was not required.

Search strategy and databases searched

Two authors (Z.G., S.M.) independently searched PubMed and Scopus from inception through July 2022. The search process involved the following terms: “preoperative,” “preventive,” “proactive,” “prehabilitation,” “optimization,” “colon,” “rectal,” “colorectal,” “surgery,” “operation,” and “procedure” combined with the Boolean operators AND/OR in order to detect all RCTs that assessed the outcome of exercise-based prehabilitation programs in adult patients who underwent colorectal surgery. Exercise-based prehabilitation was defined as “a set of interventions done before surgery that helps the patient to be prepared for post-surgical stressors and also improve their functional capacity (FC) through the exercises.”¹³ To maximize the sensitivity of the search process, we manually screened the reference lists of the initially retrieved articles to search for additional eligible articles.

After excluding duplicate studies, the abstracts were independently screened by 2 authors (Z.G., S.M.) for possibly relevant studies. Any ensuing disagreements were resolved by a third reviewer (S.D.W.). After nonrelevant studies were excluded on the basis of abstract screening, a full-text review of the remaining abstracts was conducted for completeness and eligibility of reported data, according to the predefined selection criteria.

Selection criteria

Studies deemed eligible for inclusion had to fulfill the following PICO criteria:

- P (patients): Adult patients undergoing colorectal surgery for any indication.
- I (intervention): Exercised-based prehabilitation.
- C (comparator): No prehabilitation and/or rehabilitation.

O (outcome): 30-day postoperative morbidity, readmissions, and length of stay (LOS).

We excluded studies that included pediatric patients <18 years of age, those published in non-English language, nonrandomized trials, and feasibility/pilot studies. Furthermore, all studies that were assessed as having a high or moderate risk for bias with a risk of bias 2 (ROB2) tool were excluded.¹⁴

Assessment of study quality and risk of bias

The risk of bias in the studies was independently assessed using the ROB2 tool¹⁴ by 2 authors (R.G. and N.H). Any conflicts or disagreements were resolved by consulting a third author (S.E). The characteristics of a high-quality trial were defined through an expert consensus process to develop an enhanced Cochrane ROB2 tool, specifically used for prehabilitation RCTs, where double blinding is not feasible as the patients are aware if any preoperative intervention is occurring. Thus, blinding the patients was not considered essential for assessing a study as low risk in terms of performance bias. Details about this enhanced Cochrane risk of bias 2-tool are demonstrated in Table 1. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach¹⁵ was used to grade the certainty of evidence of the outcomes as very low, low, moderate, and high on the basis of 5 parameters: risk of bias, imprecision, inconsistency, indirectness, and publication bias.

Outcomes

The primary outcome of this meta-analysis was 30-day postoperative morbidity. Secondary outcomes included readmissions, LOS, and results of functional tests as reported in the RCTs.

Statistical analysis

Statistical analyses were performed using EZR (version 1.55)¹⁶ and R software (version 4.1.2). A random-effect meta-analysis was performed and statistical heterogeneity was assessed using the I^2 statistic, which indicates low heterogeneity when $I^2 < 25\%$, moderate heterogeneity when I^2 was between 25 and 75%, and high heterogeneity when I^2 was $> 75\%$. Differences between the 2 groups were expressed as odds ratios (OR) and 95% confidence interval (CI) for the categorical variables and as the weighted mean difference (WMD) and 95% CI for the continuous variables. A random-effect meta-regression analysis of the risk factors of complications in patients who did not receive rehabilitation was conducted.

Results

Seven high-quality RCTs^{10,11,17–21} comprising 1,225 patients (707 male) were included in the meta-analysis (Figure 1). In total, 598 patients received exercise-based prehabilitation, whereas 627 patients did not receive any type of prehabilitation. Four^{10,19–21} of 7 studies bundled exercise with dietary and psychological interventions. The median duration of prehabilitation was 4 (range 2–4) weeks. The indication for surgery in all studies was colorectal cancer except for 2 studies; one included both malignant and benign conditions¹⁸ and the other included premalignant colorectal lesions (dysplasia) unresectable endoscopically.¹⁷ The type and duration of exercise intervention varied between the studies, as demonstrated in Tables II and III. Four studies compared prehabilitation and standard of care treatment and 3 compared prehabilitation and rehabilitation (Table III).

Table 1
Expert consensus on an enhanced Cochrane risk of bias-2 tool specifically used for prehabilitation RCTs*

Domain	Type of bias	Definition of low risk	Assessment	Essential
Random sequence generation	Selection	Randomization of patients using validated methodology, which included centralized, computer-based, or web-based sequence generation but excluded mechanical methods that could potentially be manipulated, such as shuffling of cards; quasi-randomization or randomization on the basis of surgeons' judgment, preference, or availability were excluded	Low risk: valid randomization methodology; High risk: none or unclear randomization methodology	Yes
Allocation concealment	Selection	Acceptable method for assigning participants to comparison groups without risk of previous knowledge of an upcoming allocation; low-risk methods include central allocation and randomly mixed block sizes	Low risk: valid allocation methodology; high risk: none or unclear allocation methodology	Yes
Baseline differences between intervention group	Selection	No significant differences between the baseline demographics of the intervention and control groups; recognition, analysis, and control of baseline differences between groups	Low risk: analysis and appropriate control for baseline differences; high risk: little or no recognition or control for baseline differences, or both	Yes
Blinding of surgeons	Performance	Blinding of surgeons performing the procedure is possible and likely to be a source of bias, as long as unblinded surgeons perform outcome assessment	Low risk: independent blinded surgeon delivering intervention; high risk: no independent blinded surgeon delivering intervention	Yes
Blinding of patients	Performance	Blinding of patients to intervention is not possible, and therefore not an important method of reducing performance bias	Low risk: patients blinded; high risk: patients not blinded	No
Analysis of groups to which they were randomly assigned	Attrition	Complete reporting of follow-up of all patients, including protocol deviations, deaths, and loss to follow-up; an intention-to-treat analysis is highly desirable; modification for loss to follow-up (ie, patients who did not complete 30-d follow-up) or in those for whom a wound could not be assessed, or in those who did not have surgery after randomization, was still considered low risk; exclusion of patients in whom wounds could be assessed (eg, incorrect allocation) and per-protocol only analysis without adequate description of patients lost to follow-up were considered to be high risk	Low risk: intention-to-treat analysis performed, or full reporting of protocol deviations and loss to follow-up; high risk: no intention-to-treat analysis performed or incomplete reporting	Yes
Missing outcome data	Loss to follow-up	Acceptable level of loss to follow-up is <20% in patients who survived at 30 d; sensitivity analysis around missing outcome data is preferable to demonstrate that missing results do not affect the overall outcome of the analysis	Low risk: loss to follow-up <20%; high risk: loss to follow-up ≥20%	Yes
Blinding of outcome assessors	Detection	Blinding of outcome assessors is essential	Low risk: blinded outcome assessor; high risk: unblinded outcome assessor	Yes
Quality assurance of outcome assessment	Outcome definition	A formal definition of Clavien Dindo or CCI	Low risk: valid definition stated; high risk: definition not stated, or invalid	Yes
Quality assurance of outcome assessment	Follow-up period predefined	Follow-up intervals were pre-defined and standardized for each participant	Low risk: follow-up defined; high risk: follow-up not defined	Yes
Quality assurance of outcome assessment	Postdischarge surveillance	A process for complication assessment was established for postdischarge assessment at time of primary outcome evaluation; reliance on ad-hoc readmissions or notes-only reviews were considered at high risk of bias	Low risk: prespecified postdischarge wound assessment plan; high risk: no prespecified postdischarge wound assessment plan	Yes
Reporting	Selective reporting	Reporting of the primary outcome matched the pre-published or registered protocol	Low risk: complete, prespecified primary outcome reporting; high risk: incomplete prespecified primary outcome reporting	Yes
Reporting	Protocol registration	The study protocol should have been published or registered on a recognized trials registry in the public domain	Low risk: protocol published/ registered; high risk: protocol not published/ registered	Yes

CCI, comprehensive complication index; RCT, randomized controlled trial.

* We defined a high-quality RCT as one that was at low risk of bias across all the domains stated previously. When the assessment was unclear, this constituted a risk of bias.

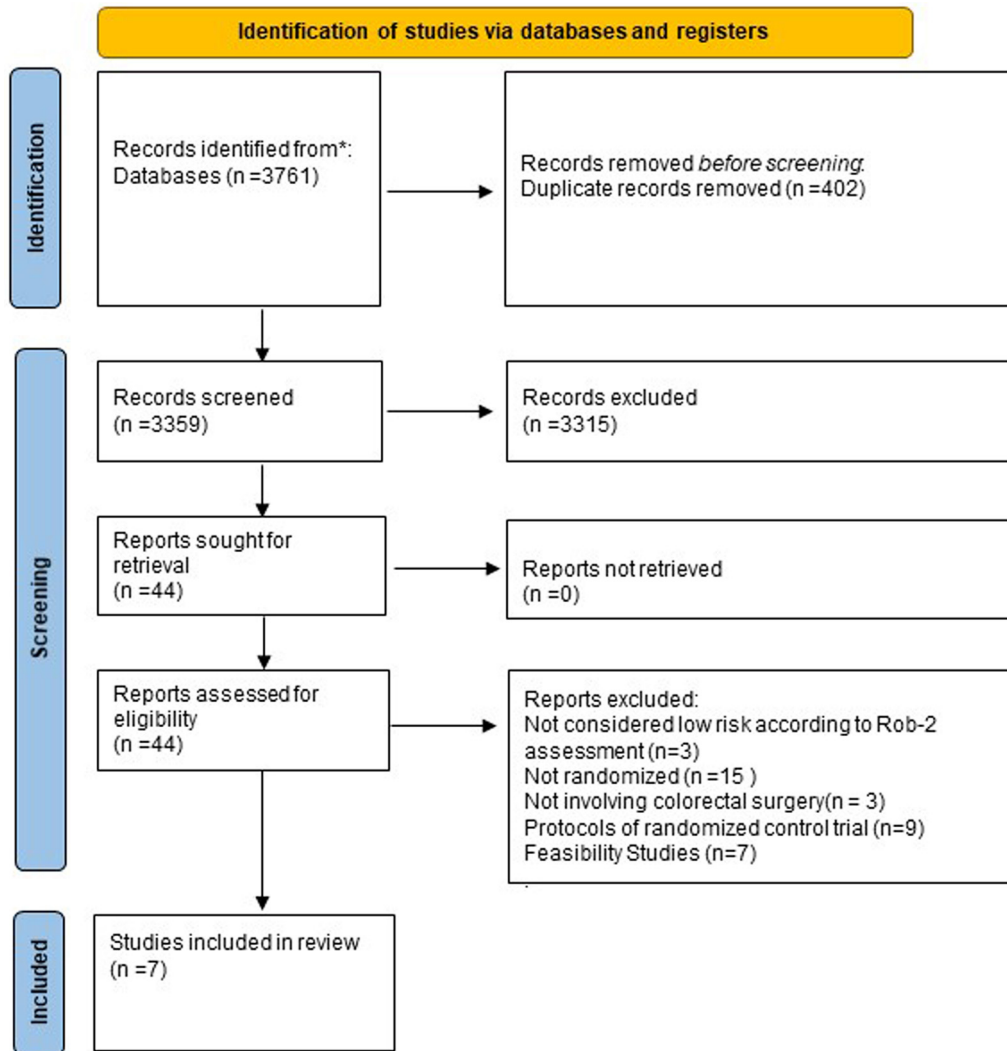


Figure 1. Prisma flowchart.

Table II
Type of exercise-based prehabilitation program and comparative arm

Study	Year	Exercise	Comparative arm
Carli et al ²¹	2020	At the hospital: 1 session/wk (30 min of moderate aerobic exercise, 25 min of resistance using elastic band(s), 5 min of stretching) with trained kinesiologist. At home: 30-min daily walk and 3×/wk elastic-band routine according to the American College of Sports Medicine guideline	Rehabilitation
Gillis et al ²⁰	2014	Done according to American College of Sports Medicine: 50-min home-based unsupervised exercise 3 d/wk alternating between aerobic and resistance training.	Rehabilitation
Bousquet-Dion et al ¹⁹ López-Rodríguez-Arias et al ¹⁰	2018 2021	Home-based exercise training + once-per-week supervised session 30–45 min at home exercise determined for each patient using Canadian Study of Health and Aging Clinical Frailty Scale; patients are guided by video playlist of aerobic and resistance training	Rehabilitation Standard treatment
Berkel et al ¹⁷	2022	Exercise was supervised by physical therapists. 60-min session of moderate-high intensity training on cycle ergometer and resistance training	Standard treatment
Onerup et al ¹¹	2022	30-min daily aerobic activity of choice at medium intensity according to Borg rating of perceived exertion scale. Inspiratory muscle training instructed by physiotherapist	Standard treatment
Peng et al ¹⁸	2021	Three elements: (1) strengthening of the upper and lower extremities; (2) thoracic and abdominal breathing exercises; and (3) exercise of abdominal muscles (mainly rectus abdominis)	Standard treatment

Table III
Duration and type of prehabilitation and patient demographics

Study	Year	Duration of prehabilitation, wk	Multimodal prehabilitation program	Number of participants		Male	
				Prehabilitation	Control/rehabilitation	Prehabilitation	Control/rehabilitation
Carli et al ²¹	2020	4	Yes	55	55	29	23
Gillis et al ²⁰	2014	4	Yes	38	39	21	27
Bousquet-Dion et al ¹⁹	2018	4	Yes	41	39	30	16
López-Rodríguez-Arias et al ¹⁰	2021	4	Yes	10	10	6	7
Berkel et al ¹⁷	2022	3	No	28	29	16	14
Onerup et al ¹¹	2022	2	No	317	351	190	210
Peng et al ¹⁸	2021	2	No	109	104	65	53

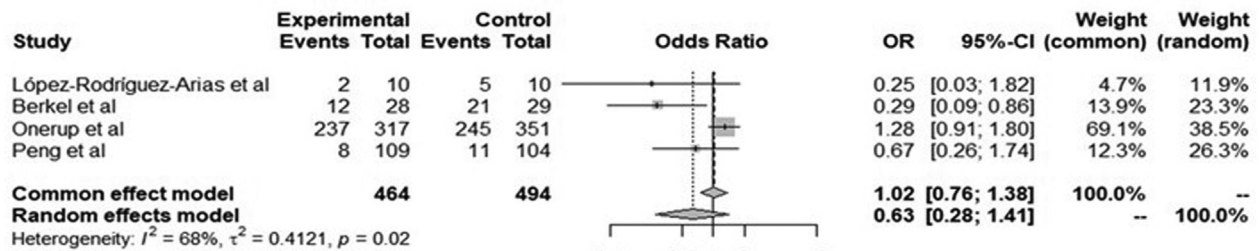
Exercised-based prehabilitation compared with standard of care

Exercise-based prehabilitation programs did not significantly reduce the odds of short-term complications (OR 0.62, 95% CI 0.27–1.40, $P = .25$, $I^2 = 68%$) or readmissions (OR 1, 95% CI 0.73–1.46, $P = .85$, $I^2 = 0%$) as compared with the standard of care

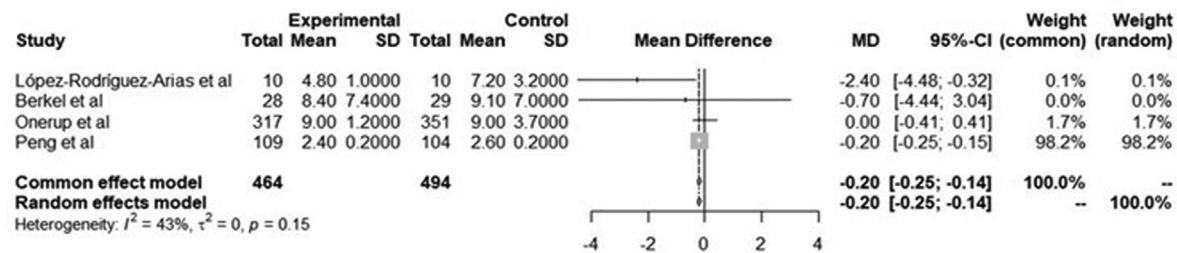
(Figure 2). Prehabilitation was associated with shorter LOS than the standard of care group (WMD -0.2 , 95% CI -0.25 to -0.14 , $P < .0001$, $I^2 = 43.3%$) (Figure 2).

Meta-regression analysis revealed that age (standard error 0.063, $P < .001$) and body mass index (BMI; standard error -0.078 , $P = .005$) were significant risk factors for complications in the

Short-Term complications



Length Of Stay



Readmissions

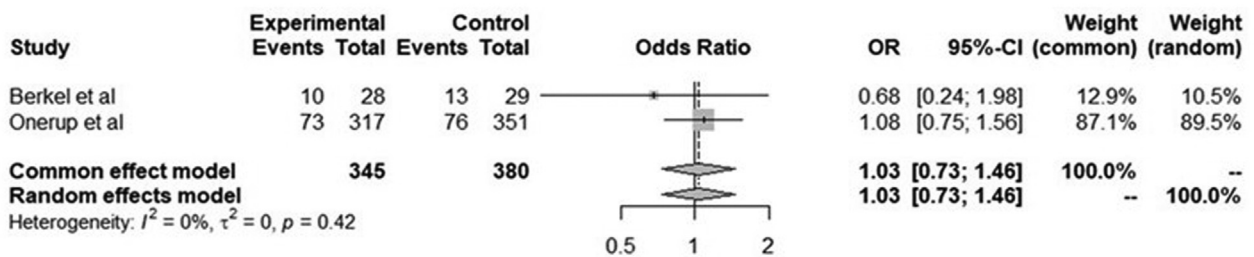


Figure 2. Forest plots for overall complication rates, length of stay, and readmission rates of prehabilitation programs compared with standard practice in colorectal surgery. CI, confidence interval; OR, odds ratio; SD, standard deviation.

control group, indicating that older patients and patients with greater BMI are at a greater risk of complications if they did not receive prehabilitation before surgery.

Exercised-based prehabilitation compared with rehabilitation

The 2 groups had similar odds of short-term complications (OR 1.03, 95% CI 0.56–1.89, $P = .91$, $I^2 = 33\%$) (Figure 3). Furthermore, there were no significant differences between the 2 groups in terms of LOS (WMD -0.16 , 95% CI -0.47 to 0.16 , $P = .33$, $I^2 = 59\%$) and the odds of readmission (OR 1.25, 95% CI 0.28–5.56, $P = .77$, $I^2 = 52\%$) (Figure 3). Prehabilitation was only superior to rehabilitation at the 6-minute walking distance test at the time of surgery (WMD -9.4 m; 95% CI -18.04 to -0.79 , $P = .03$, $I^2 = 42\%$) (Supplementary Figure 1).

Sensitivity analysis on types of complications

Only 5 studies reported data on specific types of complications.^{10,11,17,19,20} Sensitivity analyses of the type of complications did not demonstrate statistically significant differences in the incidence of pulmonary complications (OR 1.02, CI 0.72–1.43, $P = .9$, $I^2 = 0\%$), surgical-site infections (OR 1.11, CI 0.82–1.49, $P = .49$, $I^2 = 1\%$),

cardiovascular complications (OR 0.62, CI 0.35–1.09, $P = .09$, $I^2 = 0\%$), and anastomotic leaks (OR 1.4, CI 0.96–2.07, $P = .81$, $I^2 = 0\%$) between the prehabilitation/rehabilitation and control groups (Figure 4).

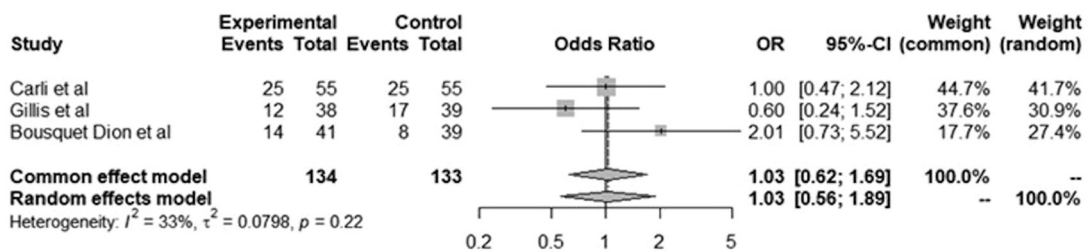
Assessment of risk of bias and certainty of evidence

As per the inclusion criteria of this meta-analysis, all studies had a low risk of bias (Supplementary Table 1). Using the GRADE approach, all the outcomes had a moderate grade of evidence certainty (Supplementary Tables S2 and S3) except for readmissions in the prehabilitation group compared with standard of care analysis, which had a high grade of evidence.

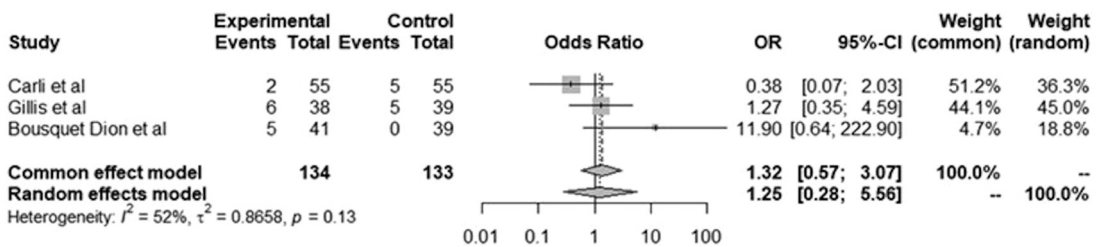
Discussion

Prehabilitation in colorectal surgery is a component of the ERAS protocol that aims to improve postoperative outcomes and shorten postoperative hospital stays. The present meta-analysis study included only high-quality RCTs on the effect of exercise-based prehabilitation programs in patients undergoing colorectal surgery. This design attempted to avoid the heterogeneity observed in previous meta-analyses^{3–7} that included nonrandomized trials and

Short-Term complications



Readmissions



Length Of Stay

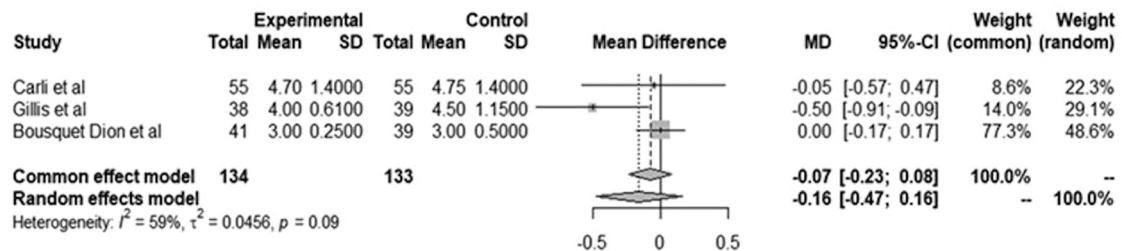


Figure 3. Forest plots for overall complication rates, length of stay, and readmissions rates of prehabilitation programs compared with rehabilitation in colorectal surgery. CI, confidence interval; OR, odds ratio; SD, standard deviation.

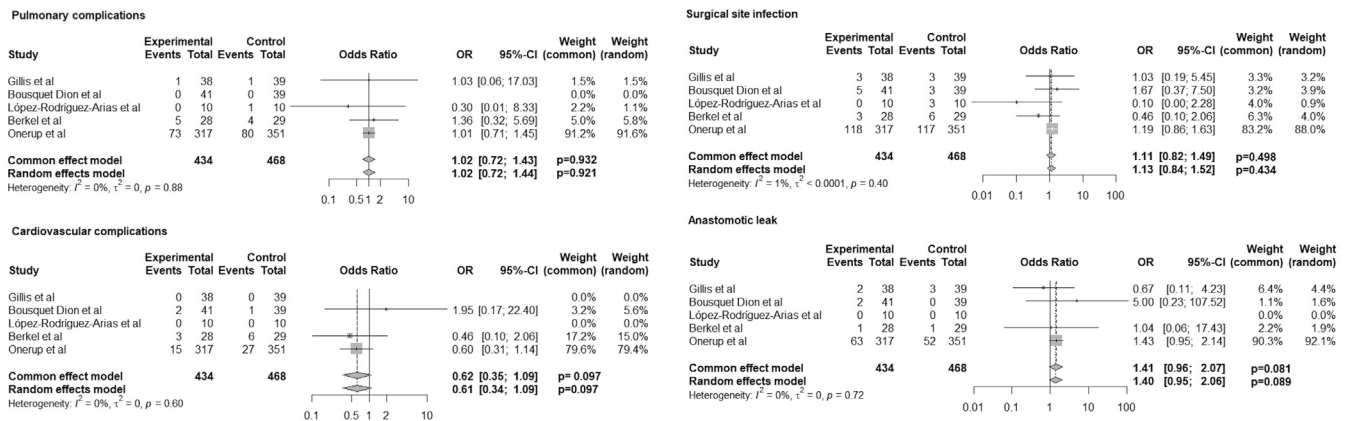


Figure 4. Forest plots for sensitivity analyses regarding types of complications. CI, confidence interval; OR, odds ratio.

trials including heterogeneous surgical procedures, rather than focusing on colorectal surgery. A Cochrane Review⁸ of RCTs that compared prehabilitation with rehabilitation did not find a significant difference in the outcomes assessed. To add to the current literature, we opted to subdivide this analysis to include comparison of prehabilitation with either a standard control (standard of care treatment) or active rehabilitation.

This analysis showed that prehabilitation was significantly associated with better functional test results at the time of surgery and shortened hospital stay. However, overall complications and readmission rates were similar to the standard of care group. This finding is important since one must consider the cost/benefit of such an intervention, especially in low/middle-income countries where the health care system can barely keep up with the high costs of a multimodal prehabilitation program.

Predictably, prehabilitation would most benefit vulnerable populations that are more prone to major postoperative morbidity including elderly patients and patients with obesity or, conversely, malnutrition. This meta-regression analysis confirmed this assumption as it showed that age and BMI are risk factors for complications when prehabilitation is not provided. Research should focus on identifying the target population that would best benefit from such a costly intervention in order to achieve the most optimal cost-benefit ratio. This need was made clear by the study of Berkel et al,¹⁷ that included only high-risk frail patients and demonstrated reduced postoperative complications in this group. Unfortunately, the rest of the studies included in this meta-analysis did not include only frail patients; thus, a sensitivity analysis for this group of patients was not feasible. Although prehabilitation might not benefit patients who are young and fit, it is possible that it may reduce postoperative morbidity in high-risk frail patients. The dilution effect of the fit population included in this analysis might explain the nonconclusive results.

Although prehabilitation managed to improve functional outcomes at the time of surgery in the control group, it was followed by similar outcomes to exercise-based rehabilitation, consistent with a previous Cochrane review.⁸ This result is compelling since a 4-week or longer prehabilitation program can delay the surgical treatment of patients with cancer, and if the benefits of prehabilitation can be still obtained when a postoperative rehabilitation program is implemented, then potential treatment delays can be avoided.

Along with a better definition of the target population for this intervention, research should strive to provide clear definitions of "better physical condition," the time needed for prehabilitation, the type of exercise, and whether unimodal compared with multimodal prehabilitation programs are the most beneficial.

Unfortunately, repetition^{22,23} of RCTs without addressing the heterogeneity of the interventions or clearly defining aims and outcomes would not add much to the current knowledge. Recently, Heil et al²⁴ identified the same problem and suggested a different design for studies on prehabilitation in colorectal surgery—the emulated target trial design, which the authors suggest can help us better assess real-world data and reinforce external validity.

This meta-analysis of high-quality RCTs demonstrated that although prehabilitation improves patients' functional scores at the time of surgery and reduces the LOS, it does not reduce complication or readmission rates. Furthermore, the postoperative clinical outcomes are similar whether the exercise program was pre- or postoperatively implemented. The current ERAS recommendations in colorectal surgery need to be reviewed regarding the potential benefit of such an intervention unequivocally over the cost in terms of financial burden, delays in surgical treatment, and lack of availability of prehabilitation programs around the globe.

Study limitations

Limitations of this meta-analysis include the heterogeneity of exercised-based interventions and of functional tests/measures for assessing physical condition and strength. Furthermore, the study population included patients who were fit and frail patients without any discrimination, which may have obfuscated the potential benefits of this intervention in the target group with the greatest need. The small number of studies available for each subgroup analysis is another limitation that reflects the limited amount of high-quality evidence on prehabilitation. There were insufficient data to perform a subgroup analysis on the types of complications and the specific effects of prehabilitation on them. In addition, because no details related to the costs associated with the prehabilitation programs used were reported in the studies, we were not able to perform a cost-benefit analysis of prehabilitation.

In conclusion, prehabilitation managed to improve functional outcomes before surgery and shorten LOS after colorectal surgery as compared with standard of care, yet it did not significantly reduce the odds of complications and readmissions. Prehabilitation and rehabilitation were associated with similar clinical outcomes.

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Conflicts of interest/Disclosures

Dr Wexner is a consultant for Baxter, Becton, Dickinson and Co, GlaxoSmithKline, Intuitive Surgical, Livsmed, Medtronic, Ostomy-Cure, Stryker, Takeda, Virtual Ports; is a member of the Data Safety Monitoring Board of JSR/WCG/ACI (chair), Polypoid (chair), and Boomerang; and receives royalties from Intuitive Surgical, Karl Storz Endoscopy America Inc, and Unique Surgical Solutions, LLC. The other authors have no related conflicts of interest to declare.

Data availability

Upon reasonable request to first author.

CRediT authorship contribution statement

Zoe Garoufalia: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Sameh Hany Emile:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Sarinya Meknarit:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Rachel Gefen:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Nir Horesh:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Peige Zhou:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Pauline Aeschbacher:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Victor Strassmann:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Steven D. Wexner:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [<https://doi.org/10.1016/j.surg.2024.07.009>].

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