Prehabilitation in patients undergoing bladder cancer surgery – A systematic review and meta-analysis

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Introduction: *The evidence on the effectiveness of prehabilitation in patients undergoing bladder cancer surgery remains lacking. Thus, the aim of this study is to determine the effectiveness of prehabilitation on reducing postoperative morbidity and length of hospital stay in patients undergoing bladder cancer surgery.*

Materials and methods: *This systematic review included randomized controlled trials investigating the effect of prehabilitation on postoperative outcomes in patients undergoing bladder cancer surgery. A comprehensive search was conducted, with two reviewers independently screening articles and extracting data. The Cochrane Collaboration's tool was used to assess risk of bias, and GRADE to rate the quality of evidence. When possible, a random effects meta-analysis was conducted. Estimates were presented as risk ratios or mean differences with their 95% confidence intervals.*

Results: *Of the 2764 articles identified, five trials comprising 282 patients met the eligibility criteria. Prehabilitation modalities included preoperative exercise (3), preoperative nutrition (1), and multimodal (1). The mean age of patients ranged from 66.0 to 72.1 years. All included trials presented some or high risk of bias. Pooled analyses according to the different prehabilitation modalities demonstrated low to very low quality of evidence of no effect on postoperative complications and length of hospital stay.*

Conclusion: *This study revealed a small number of trials investigating the effectiveness of prehabilitation on patients undergoing bladder cancer surgery. Whether prehabilitation, including preoperative exercise, nutrition and multimodal interventions reduce postoperative morbidity and length of hospital stay following bladder cancer surgery is uncertain, as the quality of evidence is very low.*

Key Words: prehabilitation, bladder cancer surgery

Introduction

Bladder cancer is the 10th most common cancer worldwide, with > 600 thousand people diagnosed each year and > 200 thousand deaths.[1] Major complex surgery, including partial or radical cystectomy, combined or with or without neoadjuvant therapy is the predominant curative treatment option.[2] The 5-year survival rates for people presenting bladder cancer range from approximately 10% (including metastatic disease) to 97% (carcinoma in situ). Overall, over 50% of people diagnosed with bladder cancer will survive 5-years or more.[3] Despite the favorable prognosis, surgical treatment is challenging and has a high rate of postoperative morbidity, with over 50% of patients experiencing at least one postoperative complication.[4] Subsequently, patients and hospitals experience increased length of hospital stay and admission cost, decreased quality of life and increased recovery time.[5] In addition, patients presenting with advanced age, obesity, history of smoking, poor physical, mental and nutritional statuses are at higher risk of postoperative complications.

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Over the last decade, prehabilitation interventions, including exercise, nutrition and/or psychological support, have been successfully employed to optimize patients' health before cancer surgery.[6] Evidence from the current literature, suggests that unimodal or multimodal prehabilitation may reduce the rate of postoperative complications, length of hospital stay and improve quality of life outcomes in patients undergoing cancer surgery.[7-9] To date, a number of randomized controlled trials have been conducted to determine the effectiveness of prehabilitation in improving postoperative morbidity and length of stay in patients undergoing bladder cancer surgery. Despite this, recent literature reviews focused on other preoperative interventions (i.e., sexual counseling, stoma education, educational training), and/or included a number of single arm non-randomized trials.[10-15] These are major limitations to the validity of the current prehabilitation evidence in bladder cancer. Thus, there is a need to comprehensively analyze and pool outcomes from the current prehabilitation trials.

Therefore, the aim of this systematic review is to determine the efficacy of unimodal or multimodal prehabilitation interventions on reducing rates of postoperative complications and length of hospital stay in patients undergoing bladder cancer surgery. The results of this review will contribute to the body of knowledge and will support future prehabilitation implementation strategies and future trials.

Materials and methods

Protocol and registration

The protocol of this systematic review and meta-analysis was written in accordance with the recommendation of the PRISMA for systematic review protocols (PRISMA-P)[16] and is publicly available at Open Science Framework (https://osf.io/). The Cochrane Handbook for Systematic Reviews of Interventions guided the conduct of this systematic review.[17]

Eligibility criteria

Studies were included if they met the following eligibility criteria: (i) randomized controlled trials investigating the effectiveness of prehabilitation (including exercise, nutrition and/or psychological interventions); (ii) reported at least one main outcome measures of postoperative morbidity and/or length of hospital stay; (iii) included a sample (or sub-sample) of patients presenting with bladder cancer and undergoing surgery. Single arm trials (e.g., intervention group only), other non-randomised study designs, and abstracts published at conference proceedings were excluded.

Information sources and search strategy

A comprehensive search strategy was developed in conjunction with an experienced librarian from the University of Sydney for Medline (Ovid), Embase (Ovid), CINAHL (Ovid), Cochrane Library PsycINFO (Ovid), and AMED (Ovid) databases. The following terms were used 'prehabilitation' AND 'bladder cancer' AND 'surgery' AND 'randomized controlled trials' AND 'postoperative morbidity OR length of hospital stay'. References of identified trials and systematic review were also checked. The search was conducted in April 2023.

Selection process and data collection

Two reviewers independently screened all identified articles using Covidence. The same reviewers independently extracted all relevant information from the eligible trials. Disagreements throughout these processes were resolved by discussion. Characteristics of the included trial, intervention, control, and outcome measures were entered into a standardized spreadsheet. When possible, the methods proposed by the Cochrane Handbook for Systematic Reviews of Interventions were used to convert extracted variables (e.g., convert median and interquartile range to mean and standard deviation).[17] The conversions were independently completed by two independent reviewers.

Risk of bias and quality of evidence

The Cochrane risk of bias tool for randomized controlled trials (RoB 2) was used to assess the risk of bias in the included trials. Each of the five risk of bias domains were rated as 'low risk of bias', 'some concerns', or 'high risk of bias'.[18]

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) was used to grade the quality of evidence within the included trials.[19] The certainty in the evidence increased or decreased accordingly to 'risk of bias', 'inconsistency', 'imprecision', and 'publication bias'. The overall quality of evidence was graded as 'very low' (i.e., the true effect is probably markedly different from the estimated effect), 'low' (i.e., the true effect might be markedly different from the estimated effect), 'moderate' (i.e., the true effect is probably close to the estimated effect), or 'high' (i.e., confidence that the true effect is similar to the estimated effect).

Two independent reviewers completed the RoB 2 and GRADE summary. Disagreements were resolved by discussion.

Synthesis methods

When possible, data were pooled via a random effects model using the Comprehensive Meta-Analysis (CMA) statistical software program. Mean difference (MD) was calculated for continuous data (e.g., length of hospital stay), and risk ratios (RR) was used for dichotomous data (e.g., rate of postoperative complications) with their 95% confidence interval (CI). RR < 1 and positive MD favored prehabilitation interventions.

Results

Study selection

The initial search identified 2764 unique articles, and five randomized controlled trials with 282 participants investigating three prehabilitation modalities, Figure 1.[20-24] The prehabilitation interventions included preoperative exercise (3 trials),[20-22] preoperative nutrition (1 trial),[24] and multimodal intervention including exercise, nutrition and psychological support (1 trial).[23] One trial included a mixed cohort of urological cancer patients (i.e., prostate, kidney and bladder cancer).[21] The sample size of the included trial ranged from 28 to 107, mostly including older male patients. Table 1 shows the characteristics of the included studies.

Risk of bias

Overall, three of the included trials were rated as 'high risk of bias' and two as 'some concerns'. The major potential source of bias was in the 'risk of bias due to deviations from the intended interventions' domain. Whereas 'risk of bias in measurement of the outcome' was rated 'low risk of bias' across all trials. Table 2 details the risk of bias assessment within the included trials.

Postoperative complications

Five trials investigated the effectiveness of preoperative exercise (3 trials; n = 196),[20-22] nutrition (1 trial; n = 28)[24]

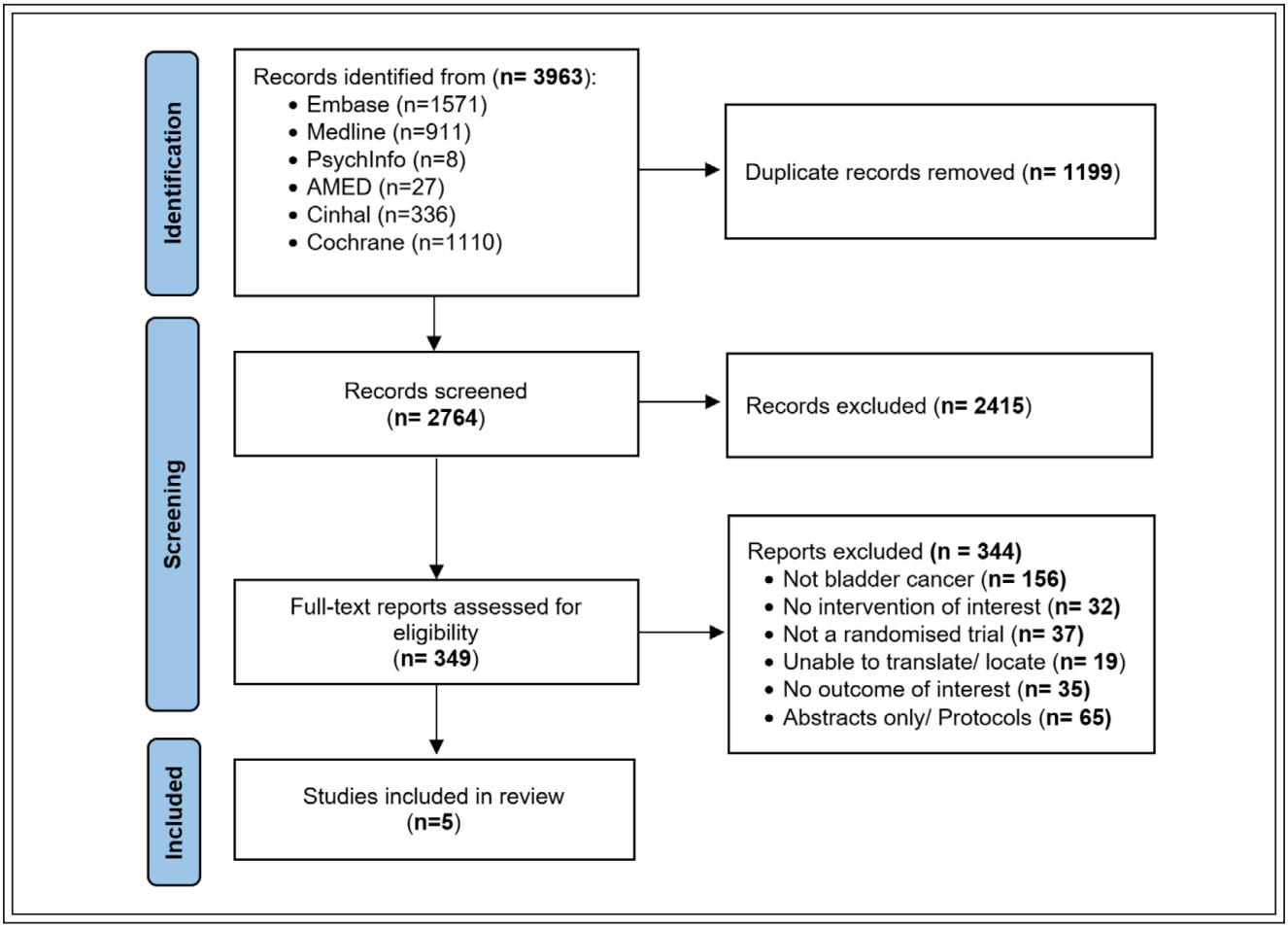

Figure 1. PRISMA flow diagram.

TABLE 1. **Detailed information of the included prehabilitation randomized controlled trials (n = 5)**

TABLE 1. Detailed information of the included prehabilitation randomized controlled trials (N = 5)

Author, yrs	Sample Characteristics	Description of the intervention group	Description of the control group	Reported outcomes
Blackwell, 2020	**Mean age (SD)**: 71.5 (3.2) **Gender, Female (%)**: 1 (3%) **Sample size**: 40	**Treatment name**: High intensity interval training (n = 19). **Description**: High Intensity Interval Training Cycle ergometer: 2 min warm-up period of unloaded cycling, followed by 5, 1-min exertions at 100-115% of the maximal load reached during their initial CPET, ending with a 2-min recovery period of unloaded cycling. **Provider**: Medical doctor. **Mode of delivery**: Face-to-face. **Location**: Exercise laboratory. **Number of times**: 12 sessions **Duration**: 4 weeks. **Intensity**: 100-115% of the maximal load reached during their initial CPET. **Tailored**: Individualized. **Adherence**: 84%.	**Treatment name**: Standard of care (n = 21) **Description**: Standard of care. **Provider**: Not applicable. **Mode of delivery**: Not applicable. **Location**: Not applicable. **Number of times**: Not applicable. **Duration**: Not applicable. **Intensity**: Not applicable. **Tailored**: Not applicable. **Adherence**: Not applicable.	**Complications**: Any complication and major complications accordingly to the Clavien-Dindo Classification (Grade>3).
Minnella, 2021	**Mean age (SD)**: 68.0 (10.3) **Gender, Female (%)**: 21 (30%) **Sample size**: 70	**Treatment name**: Aerobic, resistance training, dietary advice, oral nutrition supplementation (including protein, whey) and psychological intervention (n = 35) **Description**: Exercise (aerobic and resistance training), Nutrition (food-based intervention with/without protein supplement), Psychological (anxiety-reducing intervention). **Provider**: Exercise (Physiotherapist), Nutrition (Dietitian), Physiology (Psychologist). **Mode of delivery**: Exercise (unsupervised), Nutritional (oral), Psychological (face-to-face). **Location**: Home. **Number of times**: Exercise (3 times a week/ 65minutes), Nutritional and psychological (daily). **Duration**: 4 weeks. **Intensity**: Exercise (moderate-intensity, Borg 12-13). **Tailored**: Yes. **Adherence**: 83%.	**Treatment name**: Standard of care (n = 35) **Description**: Standard of care including risk assessment, medication management, treatment of anemia, and smoking cessation counseling. **Provider**: Not Applicable. **Mode of delivery**: Not Applicable. **Location**: Not Applicable. **Number of times**: Not Applicable. **Duration**: 4 weeks. **Intensity**: Not Applicable. **Tailored**: Not Applicable. **Adherence**: Not Applicable.	**Complications**: Any complication and major complications accordingly to the Clavien-Dindo Classification (Grade>3). **LOS**: Length of postoperative stay.

and multimodal prehabilitation (1 trial; n = 58)[23] on postoperative morbidity. No effect of preoperative exercise on any complication (RR: 0.88 [0.51 to 1.53]) or major complications defined as Clavien-Dindo Grade ≥ 3 (RR: 0.88 [0.05 to 14.06]) were observed, Figure 2. The quality of evidence was rated as very low to all postoperative complications analyzed, Table 3.

Length of hospital stay

Three trials investigated the effectiveness of preoperative exercise (2 trials; n = 162)[20,22] and multimodal prehabilitation (1 trial; n = 58)[23] on length of hospital stay in patients undergoing bladder cancer surgery. No effect of preoperative exercise (MD: 2.10 [-1.21 to 5.42]) and multimodal intervention (MD: 0.29 [-2.73 to 3.31]), when compared to control were observed, Figure 3. The quality of evidence was rated as low and very low for the preoperative exercise and multimodal intervention, respectively, Table 3.

Discussion

Summary of principal findings

This review identified five trials investigating the effectiveness of exercise, nutrition and multimodal prehabilitation on postoperative morbidity and/or length of hospital stay. Due to the limited number of trials (and small sample sizes) and the very low quality of evidence, the effectiveness of prehabilitation modalities on postoperative outcomes of patients undergoing bladder cancer surgery is uncertain.

Comparison with other studies

The findings of the current review are somewhat in line with previous reviews, however, due to our inclusion criteria (e.g., exclusion of non-randomized studies and inclusion of latest trials) and robust methodology, this review provides a more realistic estimate of the effectiveness of prehabilitation for bladder cancer patients. Most of the previous reviews describe their results in a narrative synthesis and report

TABLE 1 (cont'd). **Detailed information of the included prehabilitation randomized controlled trials (n = 5)**

Rovera, 1989	**Mean age (SD)**: 66.0 (8.1) **Gender, Female (%)**: 6 (21.4%) **Sample size**: 28	**Treatment name**: Oral nutrition supplementation (including calories, proteins, vitamins and minerals) (n = 12). **Description**: Controlled nutrition support including vitamins and minerals (PRCESION N). **Provider**: Dietician. **Mode of delivery**: Oral. **Location**: Hospital. **Number of times**: Daily (35 Kcal/day and 1.5g of protein/kg/ day). **Duration**: 10 days. **Intensity**: Not applicable. **Tailored**: Yes. **Adherence**: Not reported.	**Treatment name**: Standard of care (n = 16). **Description**: Regular hospital diet. **Provider**: Not reported. **Mode of delivery**: Oral. **Location**: Hospital. **Number of times**: Daily. **Duration**: 10 days. **Intensity**: Not applicable. **Tailored**: No. **Adherence**: Not applicable.	**Complications**: Any complication.
Banerjee, 2018	**Mean age (SD)**: 72.1 (7.6) **Gender, Female (%)**: 7 (13%) **Sample size**: 55	**Treatment name**: High intensity interval training (n = 27) **Description**: Vigorous intensity interval exercise on a cycle ergometer. **Provider**: Exercise science staff. **Mode of delivery**: Face-to-face. **Location**: Clinic. **Number of times**: Twice/ week. **Duration**: 3-6 weeks. **Intensity**: 6 x 5 min intervals (Borg 13-15/ out of 20). **Tailored**: Yes. **Adherence**: Not reported.	**Treatment name**: Standard of care (n = 28). **Description**: Standard of care. **Provider**: Not applicable. **Mode of delivery**: Not applicable. **Location**: Not applicable. **Number of times**: Not applicable. **Duration**: 3-6 weeks. **Intensity**: Not applicable. **Tailored**: Not applicable. **Adherence**: Not applicable.	**Complications:** Any complication, ileus, pneumonia, and major complications accordingly to the Clavien-Dindo Classification (Grade>3). **LOS**: Length of postoperative stay.
Jensen, 2014	**Mean age (SD)**: 70.1 (10.4) **Gender, Female (%)**: 28 (26%) **Sample size**: 107	**Treatment name**: Preoperative and postoperative strength and endurance exercises, progressive postoperative mobilization and standard of care (n = 50). **Description**: Step training on a step trainer and six different muscle strength and endurance exercises. **Provider**: Physiotherapists. **Mode of delivery**: Face-to-face. **Location**: Home-based (prehabilitation) and hospital (rehabilitation). **Number of times**: Twice daily. **Duration**: 2-3 weeks. **Intensity**: 2 x 15min intervals (step trainer), 2 x 30min intervals (mobilization). **Tailored**: Yes. **Adherence**: Prehabilitation 59%.	**Treatment name**: Standard of care (n = 57). **Description**: Standard of care including nutritional assessment, lifestyle factor education (smoking, alcohol) and comorbidity optimization. **Provider**: Not applicable. **Mode of delivery**: Not applicable. **Location**: Not applicable. **Number of times**: Not applicable. **Duration**: Not applicable. **Intensity**: Not applicable. **Tailored**: Not applicable. **Adherence**: Not applicable.	**Complications:** Any complication. **LOS**: Length of postoperative stay.

inconclusive findings. Jensen et al, conducted a systematic review investigating the efficacy of prehabilitation and rehabilitation on postoperative complications and quality of life outcomes.[12] Of the 14 studies identified (including single arm and non-randomized designs), none provided evidence to support the reduction of postoperative complications and improvement of quality of life outcomes by prehabilitation and rehabilitation interventions. Pooled analysis of perioperative nutrition interventions, from four studies (including 349 patients), compared to usual care (control) demonstrated no significant difference in postoperative complications (RR = 1.0; 95%CI = 0.69 to 1.46). In a review conducted by Piraux et al, including 360 patients (10 studies) with lung, colorectal, bladder and oesophageal cancer, endurance and resistance training exercise seemed to improve physical fitness, quality of life, decrease postoperative complications and length of hospital stay.[13] However, their conclusions were limited due to the heterogeneity within the included cancer populations. In other cancer populations, for instance lung cancer, where there is a considerable number of randomized controlled trials, prehabilitation is effective in reducing the rate of postoperative complications by half and shorten the length of hospital stay by over 2 days.[7] Therefore, future trials may change our confidence in results and effect estimates in prehabilitation for bladder cancer patients undergoing curative treatment. In addition, the use of rehabilitation (delivered within the postoperative period), may support an improved recovery and its effect should be explored further.

TABLE 2. **Risk of bias summary of the included studies**

Author, year	Risk of bias arising from the randomization process	Risk of bias due to deviations from the intended interventions	Missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall risk of bias
Banerjee, 2018	Low	High	Low	Low	Some	High
Blackwell, 2020	Low	High	Low	Low	Some	High
Jensen, 2014	Low	Low	Low	Low	Some	Some
Minnella, 2021	Low	Low	Low	Low	Some	Some
Rovera, 1989	Some	High	High	Low	Some	High

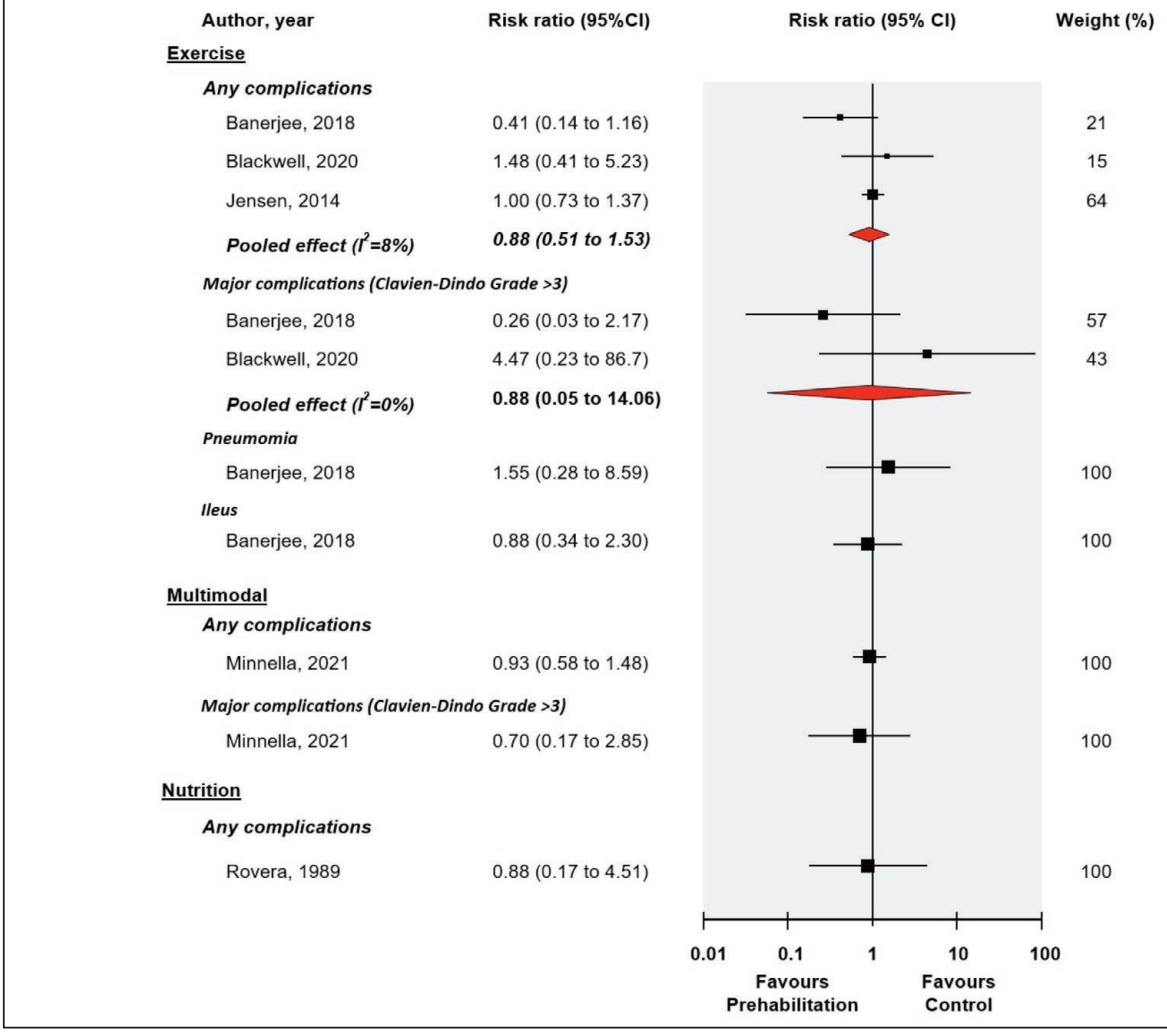

Figure 2. Risk of having a postoperative complication with prehabilitation compared to control. Risk ratio <1 favour prehabilitation interventions.

TABLE 3. **Summary of findings and quality of evidence assessment (GRADE)**

Outcomes [Author, year]	Summary of findings		Quality of evidence assessment (GRADE)				
	Sample (studies)	Effect size (95%CI)	Risk of bias	Inconsistency	Imprecision	Publication bias	Overall Quality of Evidence
Exercise trials							
Any complication [Banerjee, 2018; Blackwell, 2020; Jensen, 2014]	196 (3 RCTs)	RR: 0.88 (0.51 to 1.53)	Serious	Serious	Serious	None	⊕◯◯◯ Very low
Major complications (Clavien-Dindo ≥3) [Banerjee, 2018; Blackwell, 2020]	89 (2 RCTs)	RR: 0.88 (0.05 to 14.06)	Serious	Serious	Serious	None	⊕◯◯◯ Very low
Ileus [Banerjee, 2018]	55 (1 RCT)	RR: 0.88 (0.34 to 2.30)	Serious	Serious	Serious	None	⊕◯◯◯ Very low
Pneumonia [Banerjee, 2018]	55 (1 RCT)	RR: 1.55 (0.28 to 8.59)	Serious	Serious	Serious	None	⊕◯◯◯ Very low
Length of hospital stay (days) [Banerjee, 2018; Jensen, 2014]	162 (2 RCTs)	MD: 2.10 (-1.21 to 5.42)	Serious	Not serious	Serious	None	⊕⊕◯◯ Low
Nutrition trials							
Any complication [Rovera, 1989]	28 (1 RCT)	RR: 0.88 (0.17 to 4.51)	Serious	Serious	Serious	None	⊕◯◯◯ Very low
Multimodal trials							
Any complication [Minnella, 2021]	58 (1 RCT)	RR: 0.93 (0.58 to 1.48)	Serious	Serious	Serious	None	⊕◯◯◯ Very low
Major complications (Clavien-Dindo ≥3) [Minnella, 2021]	58 (1 RCT)	RR: 0.70 (0.17 to 2.85)	Serious	Serious	Serious	None	⊕◯◯◯ Very low
Length of hospital stay (days) [Minnella, 2021]	58 (1 RCT)	MD: 0.29 (-2.73 to 3.31)	Serious	Serious	Serious	None	⊕◯◯◯ Very low

CI= Confidence interval; RCT= Randomised controlled trials; RR= Risk ratio (value <1 favours prehabilitation interventions); MD= Mean difference (positive values favours prehabilitation interventions).

Strengths and weaknesses of the study

The current literature review has a number of limitations. The number of trials included in each meta-analysis was relatively small, and the outcome measures were vaguely defined. Most of the identified trials presented high risk of bias accordingly to the Cochrane risk of bias tool, which highlight some of the limitations within the current literature. One of the included trials included a mixed cohort of patients undergoing urological cancer surgery, including prostate, bladder and kidney cancer. The number of bladder cancer patients enrolled in this trial was very small and thus the results may not

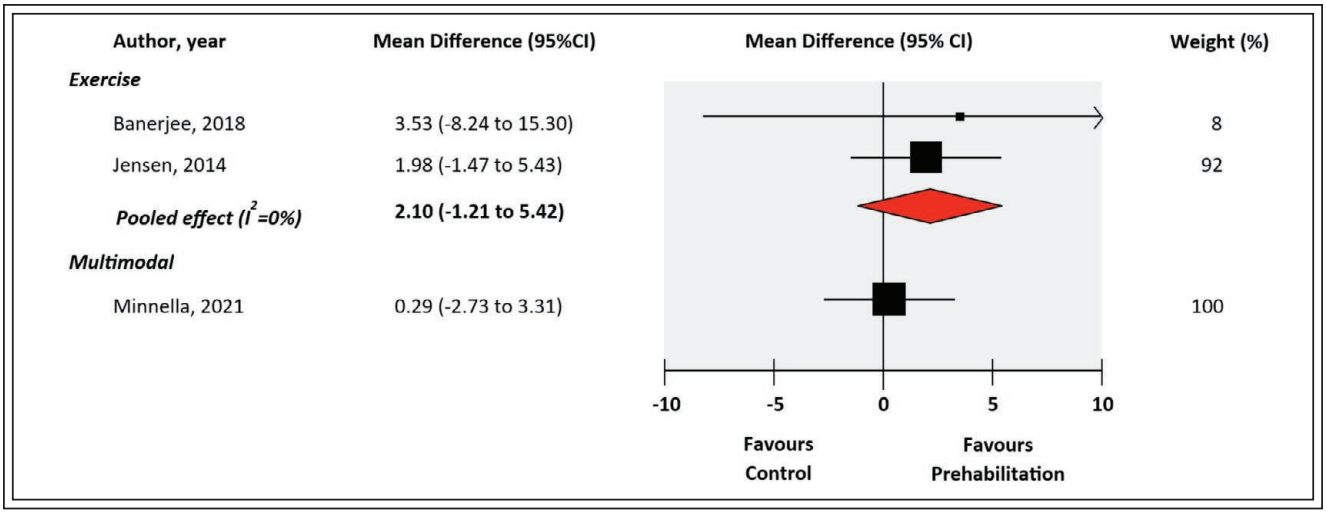

Figure 3. Pooled mean difference for length of hospital stay (days) in prehabilition randomised controlled trials for patients undergoing bladder cancer surgery. Positive values favour prehabilition interventions.

represent the bladder cancer population. The strengths of this review include the robust methodology, adhering to the Cochrane recommendations and reporting accordingly to the PRISMA statement. Another strength of our review is the conduct of meta-analysis accordingly to different prehabilitation modalities. This is one of the few reviews that conducted this statistical analysis. Finally, the use of the GRADE approach to determine the quality of the evidence is another strength of this review.

Future research

Despite the inability of our systematic review to provide a definitive conclusion on the effectiveness of prehabilitation on reducing postoperative morbidity and length of stay following bladder cancer surgery, there are a number of published protocols that will add value to the body of knowledge in the near future. The ENHANCE randomized controlled trial, will investigate the superiority of a multimodal prehabilitation program, compared to standard of care, on reducing postoperative complications in 154 patients with bladder cancer undergoing surgery in the Netherlands.[25] Whereas the STRONG-Cancer trial will compare the effectiveness of an intensive prehabilitation program, including exercise, nutrition, smoking and alcohol cessation on reducing postoperative complications and improving quality of life outcomes in 43 patients during adjuvant chemotherapy prior to bladder cancer surgery.[26] In addition, the CanMore trial will determine the effectiveness of an exercise rehabilitation program after robotic-assisted radical cystectomy in 120 patients. This trial will provide new knowledge on the utility of rehabilitation after surgical treatment for bladder cancer.[27] Further large and robust randomized controlled trials are needed to determine the efficacy of prehabilitation. Improved reporting of outcomes and detail information for the tested interventions according to the TIDieR checklist is also needed to improve transparency and reproducibility of interventions.

Conclusions

This systematic review and meta-analysis identified the need of future high quality randomized controlled trials to determine whether preoperative optimization improves postoperative outcomes for patients undergoing bladder cancer surgery. Currently, there is very low evidence of no effect of prehabilitation, including preoperative exercise, nutrition and multimodal intervention on postoperative complication and length of stay. A number of prehabilitation protocols were identified, which could change our confidence in the near future. □

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