The impact of prehabilitation on patient outcomes in hepatobiliary, colorectal, and upper gastrointestinal cancer surgery: A PRISMA-accordant Meta-Analysis

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ABSTRACT

Objective: To determine the impact of prehabilitation on hospital length of stay, functional capacity, complications, and mortality after surgery in patients with hepatobiliary, colorectal, and upper gastrointestinal cancer.

Background: "Prehabilitation" encompasses exercise, nutrition, and psychosocial interventions to optimise health before surgery. The benefits of prehabilitation are ill-defined.

Methods: Medline, Embase and Cochrane Databases were searched systematically for the terms "prehabilitation AND exercise", "perioperative care AND cancer surgery", and "colorectal AND hepatobiliary AND hepatopancreatobiliary AND oesophagogastric AND recovery AND outcomes". Primary outcomes analysed were hospital length of stay, functional capacity, significant post-operative complications (Clavien Dindo ≥ III), and mortality. A meta-analysis was conducted on the effect of all-modality prehabilitation for patients with colorectal, hepatopancreatobiliary and upper gastrointestinal cancer surgery using the raw mean difference, risk difference, and a random-effects model.

Results: 337 original titles were identified. 15 studies (randomised controlled trials; n = 9 and uncontrolled trials; n = 6) were included in the meta-analysis. Prehabilitation reduced hospital length of stay by 1.78 days versus standard care (95% CI: -3.36, -0.20, P <0.05). There was no significant difference in functional capacity with prehabilitation determined using the six-minute walk test (P = 0.816) and no significant reduction in post-operative complications (P = 0.378) or mortality rates (P = 0.114).

Conclusion: Prehabilitation was associated with reduced hospital length of stay but had no effect on functional capacity, post-operative complications, or mortality rates. Thus, prehabilitation should be recommended to accelerate recovery from cancer surgery, demonstrated by reduced hospital length of stay.

INTRODUCTION

Recently, the focus around recovery following cancer surgery has shifted towards better preparation of patients for surgery[1,2]. While enhanced recovery after surgery is now standard post-operative care[3], several studies have suggested additional benefits from increasing the cardiorespiratory fitness of patients before surgery[2,4,5]. “Prehabilitation” has gained popularity as an umbrella term to describe physical exercise, nutritional, and psychosocial interventions to optimise physical and mental health prior to major surgery [6].

Recent systematic reviews have demonstrated that prehabilitation can reduce hospital length of stay in major non-cancer surgery (e.g. bariatric surgery) [7,8] but the benefit in hepatobiliary, colorectal, and upper gastrointestinal cancer is largely unknown. These cancer patients are a unique population characterised by different clinical outcomes, length of stays, and surgical procedures. Indeed, these cancer patients may benefit significantly from nutrition and exercise programmes, as patients often present with weight loss (indicating malnourishment), and tend to be less physiologically fit than other cancer groups[9]. Collectively, this results in a hospital length of stay after oesophagectomy of 7-14 days[10], for example, whereas this is only 3.1 days after bariatric surgery [11]. Knowing whether prehabilitation reduces hospital length of stay or complication rates in cancer patients specifically is important because this can influence adjuvant therapy. Recent work has suggested that colorectal cancer patients in particular are highly resistant to the benefits of exercise[12] and thus, examining the impact of exercise and nutrition on this population is valuable.

The two most frequently studied forms of prehabilitation are exercise and nutritional interventions. It has been shown that preoperative exercise increases fitness before operation and several studies have reported improvements in cardiopulmonary exercise test variables ($\dot{V}O_{2max}$ & anaerobic threshold) and functional capacity[3,24] after supervised and unsupervised pre-operative exercise programmes[4,5,13]. Several studies have reported that improved preoperative fitness is associated with accelerated post-operative recovery following major abdominal surgery[14–18]. Benefits from prehabilitation include reduced hospital length of stay [1,19] and a reduced incidence of post-operative complications[20–22]. While no studies have reported exercise prehabilitation has a deleterious effect on post-operative outcomes, some studies have found no effect when prehabilitation is compared to standard care [20,23]. This may be a result of underpowered studies, “non-responder” effects to exercise [24], or that there is no clinically meaningful effect. Moreover, the response to prehabilitation is a complex phenomenon and whilst less fit patients are more likely to benefit most, prehabilitation does not guarantee good outcomes. Lastly, time to surgery is an independent factor that affects survival in cancer [25], and this is a major challenge to prehabilitation. Collectively, these data suggest exercise prehabilitation is capable of improving post-operative surgical outcomes, but the benefits to patients across studies and exercise-modalities remain to be determined.

Whilst there is evidence that poor nutritional status is an independent predictor of post-operative complications in colorectal cancer patients[26–29], there are few studies that have studied the possible benefits of nutritional prehabilitation for cancer surgery. It has been shown that under-nourished or ‘at risk’ patients are likely to have more post-operative complications [26], although the benefits are not always clear. Studies providing carbohydrate and protein supplementation in eucaloric populations pre-surgery have shown little benefit [30,31]. However, studies concerning protein provision have shown promising results including reduced hospital length of stay, lower rates of post-operative complications, and reduced readmission rates, regardless of baseline nutritional status [32]. The net benefit of nutritional interventions before major cancer surgery remains to be determined.

Psychosocial interventions are often implemented as part of wider multimodal prehabilitation and aim to reduce stress and anxiety through education and counselling [2,23,33,34]. Further, studies have shown psychosocial interventions can augment improvements following exercise [35] or nutritional [36] interventions. Studies examining psychosocial-prehabilitation have, however, either not reported psychology-specific outcomes [2] or showed no significant improvement in anxiety and depression scores[23,33].

Despite potential advantages of prehabilitation to improve patient outcomes after cancer surgery, the benefits relating to specific cancer types are less clear. Concerning patients undergoing surgery for colorectal, hepatopancreatobiliary, and oesophagogastric cancer, there has been no meta-analysis to provide pooled analysis of the evidence from published studies to date. Therefore, the aim of this systematic review and meta-analysis was to determine the impact of prehabilitation on hospital length of stay, functional capacity (measured by the six-minute walk test [6MWT]), post-operative complications, and mortality rates in hepatobiliary, colorectal, and upper gastrointestinal cancer.

METHODS

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines [37]. JL and LH independently conducted the eligibility assessment in an unblinded and standardised manner. Where there was disagreement, CG served as the final adjudicator. Once each database search was completed and manuscripts were sourced, all studies were downloaded into a single reference list with duplicates removed. Eligibility was assessed based on the criteria below. For eight of these studies, authors were contacted for supplementary data.

Literature search and study selection

A systematic literature search was conducted in Medline, Embase, and Cochrane databases with no start date but we included papers published to December 18th, 2019. The search was performed within all fields and terms used were “prehabilitation” AND “peri-operative care” OR "perioperative care" AND "major surgery" OR, "colorectal" OR "hepatobiliary" OR "oesophagogastric" AND "outcomes" AND "complications".

Studies that met the following criteria were included in this meta-analysis: (1) published as a full-text manuscript; (2) not a review or protocol manuscript; (3) studies involving patients undergoing elective colorectal, hepatopancreatobiliary, oesophagogastric cancer surgery, and colorectal resections for benign disease. All included studies were required to employ an intervention design and include at least one aspect of prehabilitation. Specifically, this included (i) an exercise programme for at least one week to include; aerobic, resistance, and concurrent exercise at all exercise intensities. Inspiratory muscle training (IMT) studies were also included in this category, as evidence suggests they can increase functional capacity [38] or (ii) nutritional supplementation. Three studies included in the meta-analysis provided psychosocial support including information and/or counselling in addition to the exercise and/or nutrition intervention. Additionally, descriptive data (e.g. sample size, mean, and standard deviation) must have been reported. Where these were not reported, details were requested from authors. The aim was to investigate the impact of prehabilitation on hospital length of stay, functional capacity (measured by the six-minute walk test [6MWT]), post-operative complications, and mortality rates in hepatobiliary, colorectal, and upper gastrointestinal cancer. Where studies measured multiple outcomes, they were treated as separate data points. Due to the small number of studies, subgroup analysis was not possible for the three cancer types or different exercise modalities.

Full text articles and supplementary data were reviewed to assess methodological quality of each study, using the PEDro scale, which quantifies the methodological quality[39]. Before analysis, studies were further categorised into the primary and secondary outcomes that were recorded. To assess publication bias, funnel plots for each outcome variable were computed and the Trim and Fill method applied[40].

Outcomes

From each eligible article, data were extracted for hospital length of stay, functional capacity, post-operative complications, and mortality rates by prehabilitation intervention type. Interventions were grouped into three types (i) Multimodal prehabilitation: exercise, which included both nutrition and psychosocial support, (ii) bimodal prehabilitation: exercise and nutrition or psychosocial support, and (iii) unimodal prehabilitation: exercise or nutrition alone. Exercise interventions included were; aerobic, resistance, and concurrent exercise (combined aerobic/resistance exercise) at all exercise intensities. Regimes involving supervision by a kinesiologist or physiotherapist, and unsupervised home-based exercise regimes were included. Exercise intervention duration ranged from 1 week to 4 weeks and all interventions were within the current NHS surgery targets for cancer surgery[41]. It was our intention to summarise participant characteristics to determine if baseline fitness, clinical status, or nutrition status influenced outcome variables. However, due to absence of details in participant descriptions within the original investigations, this was not possible.

Where data were missing, authors were contacted via email to provide supplementary information. A total of eight requests were sent and a 2-week period given for responses. A further reminder email was sent after this period and a further week given to respond. Three responses were received. Data were imported into a software package designed to perform meta-analyses (The jamovi project (2020), *jamovi* (Version 1.2) [Computer Software]. Retrieved from https://www.jamovi.org). Figures were prepared in jamovi and GIMP (GIMP 2.8.4, retrieved from https://gimp.org).

Data quality assessment and statistical analysis

In this meta-analysis the cumulative effect of bias can lead to overstating or understating treatment effects. The Physiotherapy Evidence Database (PEDro) scale was used to assess the risk of bias of included studies [39]. Supplemental Table 1 shows how PEDro scores were assigned based on itemised criteria. Random-effects meta-analyses were conducted, and comparisons were made between standard care and prehabilitation. For length of stay and functional capacity, raw difference in means was calculated, and for post-operative complications and mortality rates, the risk difference. Functional capacity was determined using 6MWT, as previously validated in this population[42]. Distance completed in meters was reported in all studies, and therefore we report the raw mean difference between standard care and prehabilitation. Whilst functional capacity comprises a range of functional activities, the six-minute walking distance has been studied and considered a valid and reliable measure[42].

Hospital length of stay was reported in days from the date of operation to the date of discharge. The outcome measure for surgical complications was the number of Clavien-Dindo (CD) ≥ III complications reported[22]. Grade I & II were classified as minor complications and III & IV as major complications. These outcomes were selected as clinically meaningful endpoints in the majority (all studies reported at least 1 out of these 3 outcomes; length of stay, functional capacity, and complications) of published prehabilitation studies relevant to this review. Heterogeneity was quantified with the I^2 statistic. An I^2 value of 25% was interpreted as low, 50% as moderate and 75% as high between-study heterogeneity. To determine if the length of prehabilitation was an important factor in determining patient outcomes, we completed linear regression analysis between the length of prehabilitation and hospital length of stay, functional capacity, post-operative complications, and mortality rates. Significance was set at $P < 0.05$ and data were analysed using GraphPad Prism (GraphPad Prism 8.0, GraphPad Software, Inc.).

RESULTS

Study selection

After the initial database search, 337 publications were identified. Once duplicates were removed, 157 titles and abstracts were screened for inclusion (*Fig. 1*). After initial exclusions, 50 studies were retrieved as a full text and assessed for eligibility. Of those, 35 were excluded leaving 15 eligible articles for the final quantitative analysis (*Fig. 1*).

Study characteristics

Of the 15 studies included, 9 were randomised controlled trials and 6 were uncontrolled trials (*Supplemental Table 2*). Three studies examined the effect of multimodal prehabilitation, seven studies examined bimodal prehabilitation, and five studies examined unimodal prehabilitation. For grouping studies together, it was important to assess the type, duration and intensity of exercise across studies using exercise as prehabilitation. Although type, intensity and frequency of exercise varied between studies, most reported achieving ≥ 50% maximum heart rate. In one study where two exercise interventions (low intensity vs moderate intensity/strength training)[15] were compared, the low intensity unsupervised exercise intervention was treated as the 'standard'. The meta-analysis was run with and without this study and no difference in overall outcome was observed. In studies where nutrition was utilised, nutritional optimisation was homogenous and standardised amongst studies at 1.2-1.5 g protein/kg body mass.

Effect of prehabilitation on hospital length of stay

Three studies investigated hospital length of stay and observed a significant reduction of 1.78 days (95 % CI:0.2, 3.36, P <0.05), Fig. 2. There was low heterogeneity (I^2 <0.001%) amongst studies reporting this outcome. The small number of studies limits assessment of plot symmetry and bias. Linear regression analysis showed there was no significant relationship between length of prehabilitation and hospital length of stay (R^2 = 0.99, P >0.05).

Effect of prehabilitation on functional capacity

Seven studies examined the impact of prehabilitation on functional capacity, measured by the 6MWT. There was no significant difference in functional capacity with prehabilitation (+2.82 m, 95 % CI: -20.92, 26.56, P = 0.816), Fig. 3. There was a moderate level of heterogeneity (I^2 = 31.19%). The small number of studies limits an assessment of symmetry and bias. Linear regression analysis showed there was no significant relationship between length of prehabilitation and change in functional capacity (R^2 = 0.24, P >0.05).

Effect of prehabilitation on post-operative complications

We examined the effect of prehabilitation on grade III & IV Clavien-Dindo post-operative complications as a lower rate of surgical complications might explain reduced hospital length of stay. The overall risk difference in post-operative complications was -0.02 (95 % CI = -0.07, 0.03; P = 0.378; Fig. 4), indicating that there was no significant reduction in the risk of clinically important post-operative complications following prehabilitation. There was a moderate level of heterogeneity (I^2 = 39.73%). The funnel plot demonstrates some symmetry which suggests low level of publication bias. Linear regression analysis showed there was no significant relationship between length of prehabilitation and post-operative complication rates (R^2 = 0.05, P >0.05).

Effect of prehabilitation on mortality rates

Mortality was reported in eight of fifteen studies, although two studies reported no deaths in the monitoring period and thus were excluded from the meta-analysis. The remaining six studies all recorded 30-day mortality, while one study additionally reported 90-day mortality. The overall risk difference in mortality rates was -0.09 (95% CI = -0.21, 0.02, P = 0.114, *Fig 5*), indicating there was no significant effect of prehabilitation on mortality rates. There was a high level of heterogeneity (I^2 = 98.95%). Linear regression analysis showed there was no significant relationship between length of prehabilitation and mortality rates (R^2 = 0.007, P >0.05).

DISCUSSION

Overall effect of all prehabilitation modalities

The main finding from this meta-analysis was a statistically significant reduction in hospital length of stay with a mean reduction of 1.8 days with prehabilitation. The randomised controlled trial by Barberan-Garcia et al. employed a combination of high intensity training and psychosocial motivational coaching in a population undergoing curative colorectal, liver resections, and oesophagogastric resections[33]. This study was deemed high quality and registered eight on the PEDro scale. The largest uncontrolled trial of 627 patients (77% of which were colorectal resections) used a combination of aerobic/resistance training and protein supplementation[43]. The smallest uncontrolled trial comprising pancreatic and oesophagogastric resections employed a combination of incentive spirometry, moderate intensity exercise and protein supplementation[20]. These two studies achieved lower PEDro scores of three and four, respectively. From the data it was not possible to ascertain which aspect of prehabilitation had the largest influence on the reduced hospital length of stay. In most clinical settings this phenomenon is often multifactorial, however, the data from individual studies[33,44] suggests reduced complication rates may explain the reduced hospital length of stay, although this was not confirmed in this meta-analysis. In their study of pancreaticoduodenectomies Kitahata et al. showed no difference in operation-specific complications such as delayed gastric emptying or leak rates between prehabilitation and standard care. However, the prehabilitation group had a significantly reduced median hospital length of stay (16 vs. 24 days) due to lower pulmonary complications[44].

Of the fifteen studies, eight assessed functional capacity as measured by the 6MWT. There were four[23,45–47] moderate to high quality studies (PEDro ≥ 7). There was some variation between the studies with respect to the distance at which the 6MWT was deemed clinically meaningful. For example, one study set a threshold distance of 20 metre walking distance improvement from baseline as clinically significant[46], which was based on a prior study by Antonescu et al.[48] estimating minimally clinically important differences in patients undergoing abdominal surgery. This was not specific to cancer surgery. Another study suggested that a distance improvement of at least 19 metres had to be reached[49]. This distance was thought to be clinically meaningful as it represented the measurement error in this patient cohort[42]. All four studies reported an improvement in walking distance in the prehabilitation group compared to standard care. However, this effect was sustained at 4 and 8 weeks post-operatively in only two[45,47] out of the four studies. This suggests that sustained improvements in functional capacity may relate to the type of surgery and the timing of measurements after prehabilitation (before/after surgery). Additionally, benchmarks for clinically relevant improvements may be different for different studies involving the same type of surgery. This presents a challenge in pooling functional capacity data.

While some individual studies examined reported a statistically significant improvement in functional capacity, this was not replicated in our pooled analysis. The optimum type, duration, frequency, and intensity of exercise required to observe improvements in functional capacity within this patient cohort remains elusive.

It is also unclear what the contribution of nutrition would be to the observed overall effects. A single study by Gillis et al. used unimodal prehabilitation with nutrition counselling and whey protein supplementation[46]. In this study, although an improvement in the 6MWT was observed, it was not statistically significant. The variability in response of functional capacity probably supports a tailored prehabilitation approach[50] for different types of cancer surgery. Due to the variability in exercise types, frequency, and duration it was not possible to group cancer types together to arrive at a combined effect for functional capacity. This is pertinent in cases where physiological/biological differences may affect the response to prehabilitation strategies[51,52] as well as the effect of neoadjuvant chemotherapy [53], long/short course chemoradiation [54], and pre-operative jaundice [55].

Prehabilitation interventions spanned from as little as 1 week [44] to a maximum of 6 weeks[19]. Interestingly, in this meta-analysis, there was no statistically significant relationships between the duration of prehabilitation and the improvement in patient outcomes. However, when examining hospital length of stay, there was a strong (although non-significant) correlation (R^2 = 0.99) where shorter periods of prehabilitation promoted greater reductions in hospital length of stay [43]. More studies using different lengths of prehabilitation are required to determine if this relationship is significant. Prehabilitation interventions are constrained by National Health Service cancer waiting targets (or equivalent) but encouragingly, the results from this study suggest as little as one week can benefit patient outcomes.

Effect of prehabilitation in Hepato-Pancreato-Biliary (HPB) cancer surgery

There was a total of 842 patients from six studies[5,19,20,33,44,56] that used different combinations of multimodal, bimodal, and unimodal prehabilitation. The published data suggests that prehabilitation in HPB cancer surgery results in reduced hospital length of stay, fewer post-operative complications and preservation of gastric function, although these results have not been consistent between studies. Nakajima et al. compared a prehabilitation group (exercise and nutrition) with a matched historical cohort and showed significant reductions in hospital length of stay in the prehabilitation group[19]. In a similar study design involving the analysis of a retrospective control group compared to an exercise and nutrition prehabilitation group, a reduced hospital length of stay was not observed but there was a significant reduction in

Clavien Dindo ≥ III post-operative complications[20]. This finding was replicated in another study which randomised patients to standard care or high intensity exercise and motivational interviews as the prehabilitation intervention[33]. The authors reported a significant reduction in post-operative complications, possibly explained by an increase in aerobic capacity.

In contrast Ausania et al. employed nutrition (liquid protein/carbohydrate and enzyme replacement) and exercise prehabilitation in a total cohort of 40 patients undergoing pancreaticoduodenectomy. There was no difference in post-operative complications (pancreatic leak) and hospital length of stay. However, a significant reduction in delayed gastric emptying was found in the prehabilitation group[56]. This finding may suggest that prehabilitation might improve underlying physiology[57], however, it does not translate to reduced complication rates and length of stay with the number of patients studied. If prehabilitation does improve underlying physiology, the specifics and mechanisms remain to be determined. In a large retrospective series of 576 pancreaticoduodenectomies, Kitahata et al. reported a significant reduction in pulmonary complication rates and length of stay within a supervised exercise prehabilitation programme compared to standard care historical cohort[44]. However, there was no difference in the incidence of operation specific complications such as pancreatic/biliary leak rates and specifically delayed gastric emptying as observed by Ausania et al [56].

Dunne at al.[5] examined aerobic capacity using cardiopulmonary exercise testing data in patients undergoing colorectal liver metastases resections. A four-week exercise prehabilitation programme significantly improved maximal oxygen uptake and anaerobic threshold, and quality of life, compared to a control group[5]. Collectively, these data suggest that as little as four weeks of exercise prehabilitation can exert clinically significant benefits for patients.

Effect of prehabilitation in colorectal cancer surgery

Prehabilitation studies concerning colorectal cancer have had mixed results, whereby some studies reported reduced hospital length of stay or improvements in functional capacity, but others have not. In the body of literature we reviewed, there appears to be no evidence for improvement in post-operative complications in colorectal cancer with prehabilitation. In particular, there was no difference in operation-specific colorectal complications such as anastomotic leak, ileus or wound infection[58].

A total of 1113 patients from nine studies[2,13,15,23,33,34,43,46,47] employed prehabilitation modalities. Chia et al. focused on a group of frail patients undergoing colorectal resections and employed a multimodal prehabilitation programme. Authors reported a reduced length of stay, although there were no differences in complication rates and 30-day mortality[34]. Bousquet-Dion et al. assessed functional capacity and found that prehabilitation made no difference to this measure. However, patients deemed most likely to show improvements were the sedentary cohorts as defined by the Community Healthy Activity Model Programme for Seniors questionnaire[23,59]. In a larger study involving 484 colorectal resections, Janssen et al. showed significant reductions in peri-operative delirium but there was no difference in length of stay, complications and 30-day mortality[43]. In two separate studies[46,47] involving unimodal and multimodal prehabilitation respectively, a significant improvement in functional capacity was reported with moderate and high intensity exercise, although these have also been observed in low intensity exercise[15]. These data suggest that there may be metabolic and physiological differences between patients that influence responses to prehabilitation interventions[24,52]. This raises a further question of how to select patients that might benefit the most from prehabilitation.

Effect of prehabilitation in upper gastrointestinal cancer surgery

Prehabilitation for upper gastrointestinal cancer surgery has led to improvements in functional capacity and reductions in post-operative complications. Our analysis is based on a group of 120 patients from three studies[20,33,45]. Minnella et al. studied 49 oesophagogastric resections and reported a significant improvement in functional capacity[45]. Mazzola et al. found a reduction in post-operative complications (Clavien-Dindo ≥ III) in patients enrolled on a prehabilitation programme[20]. Although Barberan et al. [33] also reported similar significant reductions in serious post-operative complications, it was not possible to isolate outcomes for upper gastrointestinal surgery patients as the group was combined with both colorectal and HPB surgery in the study. Overall, there was no difference in hospital length of stay between the standard and prehabilitation groups.

Strengths and limitations

In this study we have been able to perform a comprehensive review of the impact of prehabilitation in HPB, colorectal, and upper-gastrointestinal surgery. By the use of PEDro scoring we have managed to assess quality of included studies. However, this study is not without limitations. The most pertinent limitation of this meta-analysis was the paucity of randomised controlled trials[60]. There were nine randomised controlled trials with a PEDro score ranging 5-8, which made evaluating the efficacy of prehabilitation challenging[61]. For the exercise interventions, there were not enough studies to allow pooling of low, moderate, and high intensity exercise subgroups. These details would allow the determination of the minimum amount, type, intensity, and frequency of aerobic/strength training to improve functional capacity or clinical outcomes. Likewise, although most nutrition interventions involved protein or carbohydrate supplementation, the variability in compliance likely rendered any additive or individual effect of nutrition inconclusive[62].

Another limitation of this literature in this field is the lack of detail in reporting. Few studies reported objective measures of exercise intensity and volume. Moreover, compliance, adherence, and attendance were not reported in the majority of investigations. Therefore, it is possible that the effect on hospital length of stay was the result of analysing patients most determined, and most able to complete the programme. Hospital length of stay may not have been improved in all participants, just those who completed the prehabilitation. Intention to treat analysis and recording attendance and adherence would improve the rigour of reporting in future studies.

While the authors of analysed studies made efforts to ensure homogeneity of patient characteristics and minimise bias through randomisation and matching comparative cohorts, it is possible that inherent/confounding differences in participant characteristics could have affected outcomes. For example, the individual motivation levels of participants to complete and adhere to interventions cannot be accounted for through randomisation.

There were no studies that assessed the sole or combined effect of psychosocial optimisation and thus, further studies here are warranted. The studies that reported psychosocial intervention as part of a bimodal or multimodal prehabilitation programme provided no analysis or supplementary data to support its use. Due to the differences in the patient populations, interventions and outcome measurements we believe that the application of a random effects model meta-analysis was justified. A random-effects model also supports assigning a heavier weighting to the smaller studies that achieved a higher PEDro score. Lastly, the mortality data was associated with considerable heterogeneity, although we have used a random effects model to moderate the influence of this. Future studies should record mortality rates at standardised time-points to allow for comparison.

Summary and conclusion

Prehabilitation can effectively reduce hospital length of stay in hepatobiliary, colorectal, and upper gastrointestinal cancer surgery. There is a lack of randomised controlled trials in this population (n = 9), of which only three scored 8 or greater on the PEDro scale and two of the studies contained only 48 and 49 patients, respectively. Thus, there is a need for larger, high quality randomised controlled trials to expand the evidence base for adoption and implementation of prehabilitation programmes and provide statistical sensitivity for low incidence measures such as mortality. In particular, the type, duration, frequency, and intensity of exercise intervention needs to be standardised. Secondly, training variables appropriate for each cancer type require further examination. To improve quality and rigour of future investigations, measurement of discrete variables such as cardiopulmonary exercise test parameters[63] pre- and post-prehabilitation may provide a standardised basis for analysing improvements in cardiorespiratory fitness, which would avoid the apparent variability in selection of a clinically meaningful benchmark for improvement in functional capacity. Future studies should focus on identifying patients who would benefit most from prehabilitation and the mechanistic underpinning of any improvement in clinical outcomes. Studies should closely monitor nutrition intake to determine if the response to exercise prehabilitation is dependent upon nutritional status. Lastly, mortality should be monitored for 12 months post-surgery to determine if prehabilitation has any affect beyond 30 or 90 days.

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Figure legends and table titles

Fig 1. PRISMA flow diagram of studies selected for systematic review

Fig. 2 (a) Forest plot comparing the effects of prehabilitation on hospital length of stay. A negative value represents a shorter length of hospital stay in prehabilitation groups compared to standard care **(b)** Funnel plot of studies evaluating the effect of prehabilitation on hospital length of stay.

Fig. 3 (a) Forest plot comparing the effects of prehabilitation on functional capacity as measured by the 6-minute walk test. A positive value represents a greater distance covered in prehabilitation groups compared to standard care **(b)** Funnel plot of studies evaluating the effect of prehabilitation on functional capacity

Fig. 4 (a) The effects of prehabilitation on Clavien-Dindo ≥ III post-operative complications. A negative value represents a lower risk in prehabilitation groups compared to standard care **(b)** Funnel plot of studies evaluating the effect of prehabilitation on post-operative complications

Fig. 5 (a) The effects of prehabilitation on mortality rates. **(b)** Funnel plot of studies evaluating the effect of prehabilitation on mortality rates.

Table S1 Itemised PEDro scoring of all included studies

Table S2 Characteristics of included studies