REVIEW ARTICLE

The effect of prehabilitation on postoperative complications and postoperative hospital stay in hepatopancreatobiliary surgery a systematic review

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Abstract

Background: Increasing numbers of high-risk (older and/or frail) patients are undergoing hepatopancreatobiliary (HPB) surgery. Therefore, optimization of the patient's psychophysiological capacity by prehabilitation is rapidly gaining importance. The aim of this study was to collect all available evidence on prehabilitation in HPB surgery and determine its effects on postoperative complications and length of hospital stay.

Methods: A systematic review was performed according to PRISMA guidelines. The electronic databases MEDLINE, Web of Science, Embase, CENTRAL, clinicaltrials.gov, and the international clinical trials registry platform (ICTRP) were searched from inception to April 2020. Methodological quality of included studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias and the ROBINS-I tool.

Results: Seven articles including a total of 1377 patients were included in the quality analysis. A trend towards less complications and a shorter hospital stay was seen in the prehabilitation group, but current evidence fails to demonstrate a statistically significant difference between groups. Risk of bias in included studies was variable, and was generally scored as moderate.

Conclusion: Strong evidence for the beneficial effect of prehabilitation on clinical outcomes in HPB surgery is lacking. A trend towards less complications and shorter hospital stay was seen in the prehabilitation group.

Received 23 October 2020; accepted 22 April 2021

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Introduction

Background

Hepatopancreatobiliary (HPB) surgery has complications in up to 30–50% of patients, with mortality rates between 2 and 5%, even in tertiary referral centers.[1,2] Until recently, interventions to improve outcome in HPB surgery have mainly focused on the peri- and postoperative period. Optimization of procedures, including minimally invasive surgery, anesthesiologic techniques and postoperative care has led to a substantial improvement of outcome in gastrointestinal and HPB surgery.[3] The introduction of the enhanced recovery after surgery (ERAS) principles aimed at a further improvement of the postoperative course.[4,5] All these efforts resulted in an overall improved outcome of surgery and a shift in patient selection, with a possibility to safely operate on an increasing number of older and less physically fit patients.[6]

More recently, a paradigm shift seems to have taken place in the perioperative optimization of patients, in which patients are not only optimized post-surgery, but also in the preoperative period (prehabilitation). The postoperative period is possibly not the best phase to adopt new habits concerning nutrition and exercise, because surgical injury or stress already has been inflicted, and patients are often stressed, fatigued and anxious.[7–9] These observations are supported by studies that demonstrated that a lower preoperative aerobic fitness and overall physical

fitness of patients increase the risk for adverse outcomes in HPB surgery.[6,10–12]

All separate preoperative measures undertaken to optimize preoperative physical, nutritional and/or psychological status of patients can be integrated in a multimodal prehabilitation program, with physical exercise training and nutritional support being the most common.[13] Despite the low-quality evidence and heterogeneity in prehabilitation programs and outcomes, there seemed to be a trend towards lower complications in the prehabilitation group when pooling all patients undergoing abdominal surgery.[14] High-risk patients seem to benefit the most.[15] Prehabilitation may be able to further improve outcomes in the field of HPB surgery, which is still considered as high-risk surgery.

Objectives

The aim of this study was to evaluate currently available evidence on prehabilitation in HPB surgery and determine its effects on postoperative complications and length of hospital stay.

Materials and methods

Search strategy

This systematic review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines,[16] and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database on 13 April 2020. The study protocol was written according to the Cochrane handbook for systematic reviews and interventions (Appendix 1). An electronic search was conducted from inception to 13 April 2020 in the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (through PubMed), Web of Science, and Embase. A detailed description of search terms and literature search can be found in Appendix 2. Additionally, the database of the main international society in HPB surgery (International Hepato-Pancreato-Biliary Association – IHPBA) was searched for published abstracts and conference papers on the topic. Both ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP) portal were searched to identify ongoing studies on the topic. No restrictions regarding language or publication date were applied. Reference lists of relevant studies and reviews on the topic were searched for additional sources.

Study selection

Studies were considered eligible for inclusion in the qualitative analysis if they studied preoperative measures undertaken to optimize preoperative physical, nutritional and/or psychological status of patients (e.g. physical exercise training, nutritional support, psychological counseling, smoking cessation, optimization of endocrine and/or exocrine insufficiency, optimization of diabetic control, measures to increase preoperative hemoglobin levels or correct iron deficiency). Only studies in patients undergoing surgery of the liver, pancreas or biliary tract (benign or malignant indication) were included. Both randomized and non-randomized trials were considered eligible for inclusion. Depending on the specific study, the control group received standard of care or a different prehabilitation program than the intervention group. As prehabilitation is a multimodal concept, only one specific aspect of this concept could vary between intervention and control group. Review articles, editorials, case reports or cohort studies including fewer than five patients per specific treatment strategy, animal studies, and studies in children were excluded. Reference lists of all included articles were screened manually to identify initially missed, but relevant studies. Disagreement on eligibility was resolved after discussion.

Data extraction

Duplicates were identified and removed using Endnote software (Clarivate Analytics, Philadelphia, US). The two first authors (MD and MV) independently screened and selected studies for their eligibility according to the study protocol and specified inclusion criteria. If agreement was not reached, study eligibility was determined by the senior author.

Data collection

Of included studies and conference abstracts that met the inclusion criteria, data were collected and are presented in Tables 1–4. The primary endpoint of this systematic review was defined as postoperative complications within 30 days after surgery. Secondary endpoints were postoperative hospital stay and preoperative psychophysiological capacity or physical fitness, irrespective of the outcome measure. Studies of which no full-text was available after contacting the authors were excluded from qualitative analysis. Authors of relevant study protocols on the topic were all contacted to further specify the nature of their ongoing research and to provide, when available, preliminary results.

Assessment of methodological quality

The methodological quality of included studies was independently assessed by the two first authors (MD and MV). For randomized controlled trials (RCTs), the Cochrane Collaboration's tool for assessing risk of bias was used.[17] Selection, performance, detection, attribution, reporting and overall bias were reported as 'low risk' (green), 'high risk' (red) or 'unclear' (yellow). Non-randomized trials were scored using the ROBINS-I tool.[18] Risk of bias was defined as 'low' (green), 'moderate' (yellow) or 'serious' (red). In case of discrepancy, the risk of bias was discussed with the senior author until consensus was reached.

Results

The initial literature search yielded 2804 studies. A further search for ongoing research resulted in 53 additional studies. Authors of ongoing research were all contacted and asked to provide

Table 1 General characteristics of included studies

Authors	Year	Country	Study design	Sample size	Type of surgery	Age in years (median (IQR) or mean ± SD)	Male sex	ASA score
RANDOMIZED CONTROLLED TRIALS								
Ausania et al.[19]	2019	Spain	RCT	Total: 40 I: 18 C: 22	Pancreato-Duodenectomy	I: 66.1 (38–80) C: 65.9 (38–81)	I: 9 (50%) C: 13 (59.1%)	II-III
Dunne et al.[7]	2016	UK	RCT	Total: 34 I: 19 C: 15	Liver resection	I: 61 (56–66) C: 62 (53–72)	I: 13 (65%) C: 13 (76%)	NR
Kaibori et al.[22]	2013	Japan	RCT	Total: 51 I: 26 C: 26	Liver resection	I: 68.0 ± 9.1 C: 71.3 ± 8.8	I: 17 (68%) C: 19 (73%)	NR
Marinelli et al.[23]	2020	Italy	RCT	Total: 400 I: 200 C: 200	Pancreatic resection	Total: 62[a] 62 patients <50 years (16%) 210 patients between 51 and 69 years (53%) 122 patients >70years (31%)	Total: 212 (53%)	NR
NON-RANDOMIZED STUDIES								
Nakajima et al.[20]	2019	Japan	Propensity score-matched cohort study	Total: 172 I: 76 C: 76	HPB surgery	I: 69 (65–76) C: 69 (60–75)	I: 51 (67%) C: 53 (70%)	NR
Kitahata et al.[21]	2018	Japan	Prospective cohort study	Total: 576 I: 331 C: 245	Pancreato-duodenectomy	I: 70 (18–90) C: 70 (35–87)	I: 191 (58.4%) C: 134 (55.1%)	NR
Wang et al.[24]	2020	Singapore	Prospective cohort study	Total: 104 I: 70 C: 34	Liver resection	I: 68 (40–80) C: 66 (46–87)	I: 52 (74%) C: 25 (73.5%)	II-III
CONFERENCE ABSTRACTS								
Bui et al.[25]	2019	Canada	RCT	Total: 35 I: 17 C: 18	HPB surgery	NR	NR	NR
Van Wijk et al.[26]	2020	The Nether-lands	Prospective cohort study	Total: 13	Liver and pancreatic surgery	NR	NR	NR
George et al.[27]	2018	United Kingdom	Prospective cohort study	Total: 11	Pancreatic resection	NR	NR	NR

IQR: interquartile range; SD: standard deviation; ASA: american society of anesthesiologists; RCT: randomized controlled trial; I: intervention group; C: control group; NR: not reported; HPB: hepatopancreatobiliary.
[a] Mean age of the study population reported in full-text, IQR not reported.

preliminary results, which added 3 studies to the search. The process of evidence acquisition is depicted in the PRISMA flow diagram (Fig. 1). Eventually, 7 original articles were included in the quality analysis.[6,19–24] Preliminary results on the prehabilitation program of three study groups were identified through conference abstracts. These trials met the predefined inclusion criteria, yet were excluded from quality analysis, because no definitive results of these studies were available at the time of this publication.[25–27] However, preliminary results of these studies were included in the overview of results.

Included studies were published between 2013 and 2020. Sample sizes varied between 34 and 576, and resulted in a total of 1377 included patients. Studies investigated prehabilitation in patients scheduled for liver surgery (n = 3), pancreatoduodenectomy (n = 2), any type of pancreatic resection (n = 1) and any type of HPB surgery (n = 1). General study characteristics can be found in Table 1. Four RCTs and 3 non-randomized studies were included. Included patients had a median age that varied between 61 and 71 years and, when reported, ASA scores of II-III. None of the papers reported on demographics of patients that were not

Table 2 Characteristics of prehabilitation program

Authors	Uni- or multimodal	Physical exercise training	Nutritional support	Psychological support	Assistance in smoking cessation	Adherence (in %)	Reasons for drop-out	Specific postoperative care
RANDOMIZED CONTROLLED TRIALS								
Ausania et al.[19]	Multimodal	Yes	Yes	No	Yes	NR	NR	ERAS
Dunne et al.[7]	Unimodal	Yes	No	No	No	94.7%	Progression of other disease Preferred prehabilitation group Unresectable disease	NR
Kaibori et al.[22]	Multimodal	Yes	Yes	No	No	NR	NR	Program continued postoperatively
Marinelli et al.[23]	Unimodal	No	No	Yes	No	28.5%	Randomization not possible due to logistic reasons	NR
NON-RANDOMIZED STUDIES								
Nakajima et al.[20]	Multimodal	Yes	Yes	No	No	70.4%	Withdrew consent No exercise recorded Unresectable disease	NR
Kitahata et al.[21]	Unimodal	Yes	No	No	No	NR	NR	ERAS
Wang et al.[24]	Multimodal	Yes	Yes	Yes	No	NR	NR	None
CONFERENCE ABSTRACTS								
Bui et al.[25]	Multimodal	Yes	Yes	Yes	No	NR	NR	Program continued postoperatively
Van Wijk et al.[26]	Unimodal	Yes	No	No	No	42.0%	Logistics Severe comorbidity Time schedule	NR
George et al.[27]	Multimodal	Yes	Yes	No	No	100%	None	NR

NR: not reported; ERAS: enhanced recovery after surgery.

included. The only study focusing on high-risk patients was the study of Kaibori *et al.*,[22] as they studied a perioperative training program for patients with liver cirrhosis undergoing surgery for hepatocellular carcinoma (HCC). In this study of the 51 included patients, 49 had a Child-Pugh A cirrhosis.

Components of prehabilitation

Characteristics of the prehabilitation programs are listed in Table 2. More than half of the included studies (4/7) investigated a multimodal prehabilitation program.[19,20,22,24] In all but one,[23] physical exercise training was part of the intervention. In the study published by Marinelli *et al.*,[23] the intervention consisted only of a brief psychological intervention on the day before surgery. Due to several logistic and organizational pitfalls, drop-out in this study was extremely high (71.5%). Only two other studies reported on adherence to the prehabilitation program and reasons for drop-out.[7,20]

Physical exercise training intervention

Details on various physical exercise training interventions can be found in Table 3. Both location of training and level of supervision varied among the included studies. In 2 studies,[21,7] physical exercise training took place in the hospital; one study offered partly hospital-based training.[19] In the remaining trials, physical exercise training took place in a home-based setting. Along with the location of training, the level of supervision varied highly. As mentioned, in 3 studies training took place in the hospital. However, the level of education of supervisors was not reported in 2 of them.[19,7] In 2 studies in which home-based training was performed, physical therapists monitored adherence to the training in a retrospective manner.[20,22] In one study, training was not supervised.[24]

Training frequency varied between twice daily and 3 times a week. Duration of physical exercise training preoperatively ranged from one week[21] of training in the hospital to a median of

Table 3 Details of physical exercise intervention

Authors	Location	Supervision	Frequency of training	Period of prehabilitation	Type of physical exercise training
RANDOMIZED CONTROLLED TRIALS					
Ausania et al.[19]	Partly hospital-based (5 days of training) Partly home-based	Partly supervised (5 days of training in outpatient clinic)	Daily	Variable Median duration of prehabilitation: 12.6 days	High-intensity endurance training on stationary cyclo-ergometer bicycle. Each session: 10min warming-up, 20min muscle toning, 20min aerobic exercise, 10min cool-down. Breathing exercises. *Personalized based on individual needs after multidisciplinary assessment*
Dunne et al.[7]	Hospital-based	Supervised	3 times a week	4 weeks	Warming-up, cool-down, 30min interval training altering in exercise intensity using cycle ergometer. *Personalized on individual oxygen uptake at the AT*
Kaibori et al.[22]	Home-based	Partly supervised (confirmation by physiotherapist, once or twice a month)	3 times a week	Variable Up to 1 month preoperatively, until 6 months postoperatively	Personalized training, including 5 min stretching, 30 min walking, 20 min targeted stretching, 5 min cooling-down. *Personalized on individual oxygen uptake at the AT*
NON-RANDOMIZED STUDIES					
Nakajima et al.[20]	Home-based	Partly supervised (confirmation of training by physical therapist upon admission)	Minimum of 3 times a week	Variable Median duration of prehabilitation: 32 days	Aerobic (walking, at least 30min) and resistance training (walk, sit-ups, squats, calf raises, bridge-ups, upper-limb movement). *Not personalized*
Kitahata et al.[21]	Hospital-based	Supervised (training in central rehabilitation room)	Twice daily	7 days	Aerobic and strengthening training (ergometer, treadmill, stepping the stairs), Muscle strengthening (squats) and breathing training (abdominal breathing and bronchial drainage). *Personalized on 'individual body function and comorbidity'*
Wang et al.[24]	Home-based	Unsupervised	Daily	Variable Between 2 and 4 weeks before surgery	Respiratory muscle training (4 times a day for a minimum of 10 breaths) Lower limb strengthening exercises and a walking program (30 min, 5 times a week). *Not personalized*
CONFERENCE ABSTRACTS					
Bui et al.[25]	Home-based	Partly supervised (supervised training once weekly)	NR	4 weeks	NR
Van Wijk et al.[26]	Home-based	Partly supervised (not specified in abstract)	3 times a week	4 weeks	NR
George et al.[27]	NR	NR	3 times a week	4 weeks	High-intensity interval and resistance training

AT: anaerobic threshold; NR: not reported.

Table 4 Outcome measurement

Author	Preoperative improvement in functional capacity or physical condition in prehabilitation group	Postoperative complications[a]	Length of hospital stay in days (median (IQR))	In-hospital mortality	30-day readmission rate
RANDOMIZED CONTROLLED TRIALS					
Ausania et al.[19]	FEV_1 and FVC: 20% improvement after prehabilitation[b] Dynamometer strength test: 16–21% improvement 10-m walk test: 19% improvement	Type I-II I: 6 (33.3%) C: 12 (54.5%) Type III-IV I: 4 (22.2%) C: 5 (18.2%) p = 0.751	I: 11.4 (7–46)[d] C: 13.2 (7–60) p = 0.449	NR	I: 1 (5.6%) C: 2 (9.6%) p = 0.673
Dunne et al.[7]	Improvement in oxygen uptake at AT: 1.9 ml/kg/min (0.1,3.6) p = 0.037[e]	Type I-II[b] I: 5 (26%) C: 6 (40%) Type III-IV[b] I: 3 (16%) C: 1 (67%)	I: 5 (4–6)[b] C: 5 (4.5–7)	NR	I: 4[b] C: 0
Kaibori et al.[22]	NR	Type I-IV I: 2 (8.7%) C: 3 (13%) p = 0.67	I: 13.7 ± 4.0[f] C: 17.5 ± 11.3 p = 0.12	0	NR
Marinelli et al.[23]	NR	Type I-IV I: 47.7% C: 55.9% P = 0.48	I: 12.5 ± 12.0[f] C: 13.5 ± 14.1 p = 0.62	NR	NR
NON-RANDOMIZED STUDIES					
Nakajima et al.[20]	6-MWT (pre- vs post-prehabilitation): 530 vs 554 m p < 0.001 Muscle/fat ratio: 1.75 vs 1.83 p < 0.001[c]	Type III-IV I: 32 (42%) C: 38 (50%) p = 0.329	I: 23 (16–34) C: 30 (21–40) p = 0.045	0	NR
Kitahata et al.[21]	NR	Type III-IV I: 61 (18,9%) C: 54 (22%) p = 0.239	I: 16 (7–130)[d] C: 24 (7–223) p < 0.001	I: 1 (0.3%) C: 2 (0.8%) p > 0.999	NR
Wang et al.[24]	NR	Type I-II I: 28 (72%) C: 21 (78%) Type III-IV I: 10 (26%) C: 5 (19%) p = 0.02	I: 6 (0–51)[d] C: 8.5 (2–25) p = 0.21	NR	I: 4 (5.7%) C: 3 (8.8%) p = 0.55
CONFERENCE ABSTRACTS					
Bui et al.[25]	6-MWT: Improvement of 19.6 m p = 0.061	NR	NR	NR	NR
Van Wijk et al.[26]	Improvement in oxygen uptake at AT in 6/11 patients (54%): median 1.6 ml/kg/min, IQR 1.0[b]	NR	NR	NR	NR
George et al.[27]	Improvement in oxygen uptake at AT: median 1.68 ml/kg/min p = 0.014 No difference in handgrip strength p = 0.098	NR	NR	NR	NR

FEV_1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; I: Intervention group; C: Control group; NR: Not reported; 6-MWT: 6-min walk test; AT: Anaerobic threshold.
[a] According to the Clavien-Dindo classification.
[b] Statistical significance not reported.
[c] Other outcomes reported in full-text article: Knee extension strength, grip strength, 10-m usual walking speed, total skeletal muscle mass, total fat mass.
[d] Reported as median (range).
[e] Other outcomes reported in full-text article: Oxygen uptake at peak, oxygen pulse at AT, oxygen pulse at peak, peak work rate, heart rate reserve and quality of life using SF-36 scores (Short-Form 36, QualityMetric, Lincoln, Rhode Island USA).
[f] Reported as mean ± standard deviation.

32 days of preoperative training at home.[20] Details on the type of physical exercise training can be found in Table 3. Two studies offered non-personalized training.[20,24] In the trials of Dunne *et al.*[7] and Kaibori *et al.*[22] training was personalized based on the oxygen uptake at the anaerobic threshold. Two other studies[19,21] tailored training based on 'individual needs' or 'body composition', although this was not further specified. Objective monitoring of training progression was not reported in any study.

Outcome measurement

Outcomes reported in the included studies are summarized in Table 4. Only 3 of the included studies reported test results of physical fitness before and after prehabilitation. There was major heterogeneity in the used outcome measures. Dunne *et al.*[7] used results of cardiopulmonary exercise testing (CPET) before and after prehabilitation, Nakajima *et al.*[20] used the 6-min walk test (6-MWT) and calculation of the muscle/fat ratio and Ausania *et al.*[19] used results of spirometry, a dynamometer strength test and a 10-m walk test to monitor physical fitness. In all of them, a statistically significant improvement was seen after prehabilitation. The three groups that reported preliminary results used the 6-MWT[25] and CPET[26,27] to monitor the effect of prehabilitation.

Due to the limited number of included studies and heterogeneity of the data, no complete meta-analysis of available data or subgroup analysis was performed. However, a pooled analysis of the results of included RCTs regarding postoperative complications (Clavien-Dindo I-IV) and postoperative hospital stay is depicted in Figs. 2,3. Regarding major postoperative complications (defined as Clavien-Dindo III-IV[28]), only one study[24] noted a significant decrease in the prehabilitation group. One study reported a statistically significant decrease in delayed gastric emptying,[19] one group described a lower incidence of bile leaks,[20] and one study noted a significant decrease in pulmonary complications in the prehabilitation group.[21] No statistically significant reduction in overall complications could be noted in the prehabilitation group. Median length of postoperative hospital stay ranged from 5 to 30 days. A statistically significant decrease in hospital stay in the prehabilitation group was seen in two of the included studies, yet pooling of results could not show an overall statistically significant reduction.[20,21]

Three of the included studies reported on the effect of prehabilitation programs on quality of life. Dunne *et al.*[7] noted a trend towards improvement of overall quality of life in the prehabilitation group, although this was not statistically

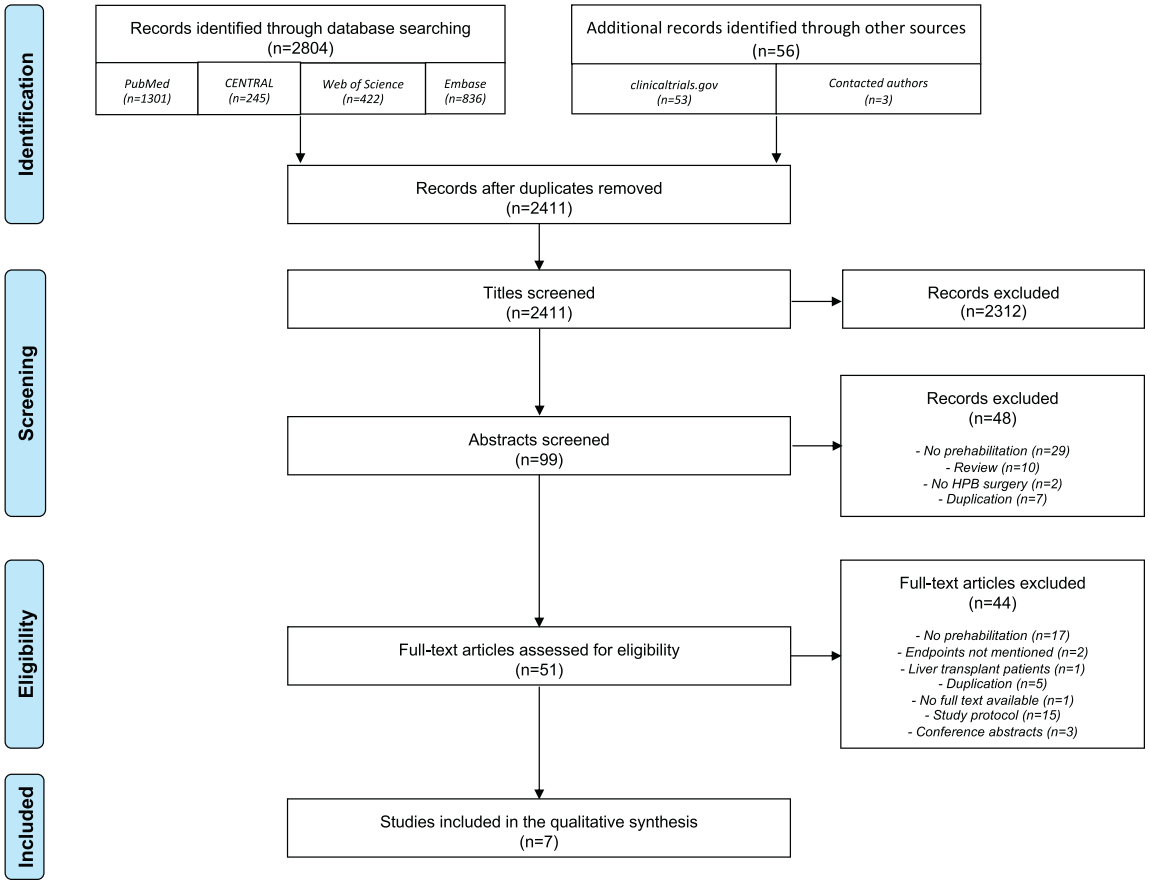

Figure 1 PRISMA flow diagram

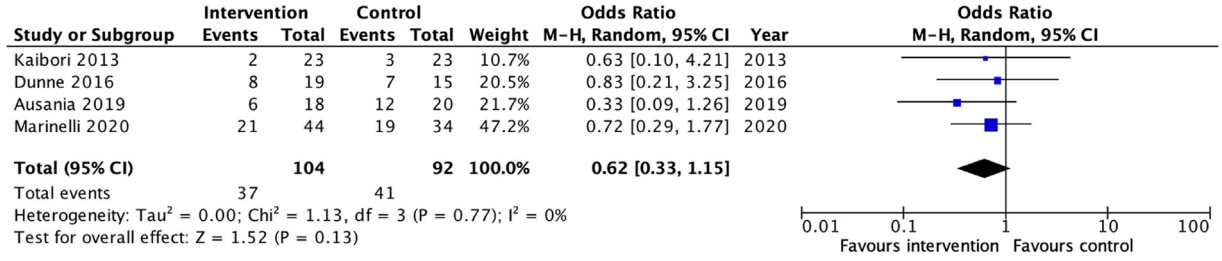

Figure 2 Forest plot for postoperative complications (Clavien-Dindo I-IV)

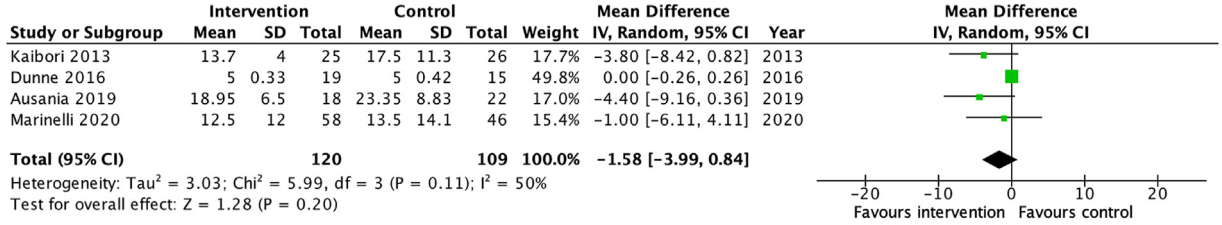

Figure 3 Forest plot for length of postoperative hospital stay

significant (p = 0.140). The group of Marinelli *et al.*[23] reported a significant improvement of the emotional well-being in the patient group that underwent preoperative psychological intervention. This was confirmed by Wang *et al.*,[24] who reported a significant improvement of the social and family well-being after prehabilitation, when compared to the control group.

Methodological quality

Results of the quality analysis of included studies are summarized in Table 5. Generally, there is large variability in the risk of bias of included studies. Performance bias was a main concern in all studies, because blinding of participants was difficult to achieve. The overall risk of bias in Ausania *et al.*[19] was scored high, because the full-text article failed to unquestionably provide some vital information on the methodology. Overall risk of bias in the study by Marinelli *et al.*[23] was scored high because of major concern on the high rates of drop-out, and considerable levels of detection and attribution bias. Generally, risk of bias of included non-randomized studies was considered moderate. Risk of bias was scored as 'serious', because exclusion criteria were not defined in the full-text[21] and important baseline characteristics of patient groups differed significantly.[24]

Discussion

Main results

Current evidence failed to demonstrate a significant reduction of postoperative complications in patients that underwent prehabilitation, yet a pooled analysis showed a trend towards complication reduction. All included studies revealed a trend towards a reduction in postoperative hospital stay, with 2 of the included studies providing a statistically significant difference.[20,21] Regarding the effect of prehabilitation on (in-hospital) mortality and readmission rates in HPB surgery, no conclusions can be drawn from included studies. Probably these studies were also underpowered to be able to show statistically significant results for these outcome parameters. These findings are consistent with current literature outside HPB surgery, although some (small) studies in the field of thoracic and colorectal surgery have shown a significant reduction in postoperative complications after prehabilitation.[6,15,29–32]

Several studies investigated the correlation between preoperative fitness and postoperative outcomes in HPB surgery. For example, Hayashi *et al.* identified a correlation between major postoperative complications and results of a preoperative 6-min walk test (6-MWT) in patients that underwent HPB surgery.[10] Junejo *et al.* identified the oxygen uptake at the anaerobic threshold, assessed by cardiopulmonary exercise testing (CPET), as a prognostic adjunct in identifying high-risk patients in hepatic resection.[11] These results were confirmed by Ausania *et al.* in a group of patients who underwent pancreatoduodenectomy.[12] When reported, included studies in this review did show an improvement of physical fitness in prehabilitated patients.

Lessons learned from included studies

Heterogeneity, in the context and content of prehabilitation programs, as well as in the outcomes to measure its effect, seems the main reason for inconsistent results and limited quality of evidence.

The definition of prehabilitation varies highly in included studies (Table 2). Physical exercise training and nutritional support are the cornerstones of most multimodal prehabilitation programs, whereas psychological interventions and support in

Table 5 Quality analysis of included studies

Randomized controlled trials - Risk of bias based on Cochrane Collaboration's tool for assessing risk of bias[17]

Author	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participant (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attribution bias)	Selective reporting (reporting bias)	Other bias	Overall bias
Ausania et al[19]	Unclear	Unclear	High risk	Unclear	Unclear	Low risk	Small number of included patients	High risk
Dunne et al[7]	Low risk	Low risk	High risk	Unclear	Low risk	Low risk	Small number of included patients, young study population	Low risk
Kaibori et al[22]	Low risk	Unclear	High risk	Unclear	Low risk	Low risk	Small number of included patients	Low risk
Marinelli et al[23]	Low risk	Low risk	High risk	High risk	High risk	Low risk	Major drop-out due to logistic reasons	High risk

Non-randomized studies - Risk of bias based on ROBINS-I tool[18]

Author	Bias due to confounding	Bias in selection	Bias in classification of intervention	Bias due to deviations from intervention	Bias due to missing data	Bias in outcome measurements	Bias in reported results	Overall bias
Nakajima et al[20]	Moderate risk	Low risk	Moderate risk	Moderate risk	Low risk	Moderate risk	Low risk	Moderate risk
Kitahata et al[21]	Low risk	Moderate risk	Serious risk	Moderate risk	Low risk	Moderate risk	Moderate risk	Moderate risk
Wang et al[24]	Serious risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk

smoking cessation are only rarely part of the intervention. The main argument to offer prehabilitation as a multimodal intervention is the synergy between its elements. Some authors stress the importance of a psychological intervention as a vital part of prehabilitation, mainly because it may influence coping with complications, postoperative hospital stay, postoperative pain and, hence, quality of life.[8,23,24,33] A systematic review of Thomsen *et al.* reported on the ability of smoking cessation interventions to reduce postoperative complications. However, until recently, it was only rarely part of prehabilitation programs.[8,34] Only one study included a systematic correction of exocrine and endocrine pancreatic insufficiency in patients undergoing pancreatic surgery as part of their prehabilitation program.[19] This is now considered best practice,[35] and should probably be part of any prehabilitation program that includes patient with pancreatic cancer.[36]

Regarding the context and contents of physical exercise training interventions, heterogeneity is again a major concern. Both training location and level of supervision vary greatly between included studies. Hospital-based training offers the advantage of better monitoring, but comes at a price of higher costs, patient burden and logistic problems. In the study by Dunne *et al.*, several patients refused to participate because of the distance to the hospital, where training took place.[7] Transport to the hospital may offer specific problems for elderly and frail patients, who might benefit the most from prehabilitation. In 3 of the included studies, training took place at home.[20,22,24] Home-based training has the advantage of accessibility, lower cost and allows patients to develop skills of training in the setting to which they will return soon after surgery,[7,9] but may pose problems with the level of supervision. In one study training was unsupervised, one study included telephonic supervision of adherence, and in one study training was confirmed retrospectively upon admission.[20,22,24] This problem of supervision in home-based training can be addressed by implementation of a network of trained and competent community physical therapists in the catchment area of the hospital who provide direct supervision, or by the concept of telemonitoring.[7,9] Regarding contents, the short preoperative period requires high-intensity training and should be targeted to elicit overload in order to improve physical fitness in short term.[37,38] It is generally unclear whether training programs of included studies focused sufficiently enough on highly intensive training to maximize effects, which may have led to false negative results. Thereby, monitoring of training progress was not reported in any study, which is important to motivate responders, timely identify non-responders, and make necessary personalized program adjustments.[39]

Included studies generally did not focus on high-risk patients.[7,9,38] Some studies even excluded some of them due to the inability to perform the proposed physical exercise training program. Physical exercise training was not personalized in 2 of the included studies.[20,24] In the remaining studies, training was personalized based on CPET (n = 2)[7,22], after multidisciplinary assessment (n = 1)[19], and based on individual body function and comorbidities (n = 1)[21]. A more tailored approach with a more profound personalization of physical exercise training in the living environment of the patient may lead to an increased proportion of high-risk patients being able to undergo prehabilitation, which meets the demands of a changing population undergoing HPB surgery. Whether personalization should be based on results of CPET, body composition or other variables, remains a matter of debate.[9]

Primary and secondary outcomes vary highly among included studies. Of the 3 studies reporting on an improvement of preoperative physical fitness after prehabilitation and prior to surgery, one study used results of spirometry,[19] one study used results of CPET[7] and one study used results of a 6-MWT.[20] One of the aims of the systematic review by Thomas *et al.*[9] was to identify the optimal postoperative outcome measure to assess effects of prehabilitation in intra-abdominal cancer surgery. They stated that merely measuring incidence of postoperative complications does not adequately reflect the effect of prehabilitation, as they may occur equally in prehabilitated and/or fitter patients, but its impact may not be as severe. They believe that an outcome measure in which the impact of a complication is also considered (use of resources, length of hospital stay) better describes this 'resilience', and should be used to investigate potential benefits from prehabilitation.[9,39,40] As opposed to postoperative complications, results of this review did show more consistent results regarding length of hospital stay, favoring the prehabilitation group.[41] Finally, most studies have small patient groups, and lack a power analysis.

Limitations of this review

Since the aim of this review was to collect all currently available data, broad inclusion criteria were used and non-randomized studies were also included in the analysis. Only limited data on the topic was available, and therefore a full meta-analysis of all outcome parameters could not be performed. A subgroup analysis of elderly patients that was defined in the review protocol was not performed for the same reasons.

In the current era, randomization in studies investigating prehabilitation has specific limitations. First, one could assume that all patients undergoing HPB surgery have some sort of prehabilitation and preoperative optimization, regardless of the study arm, as this is common practice in most specialized centers. Second, most patients prefer prehabilitation or start initiatives to improve their psychophysiological capacity themselves, which makes a randomized-controlled setting difficult and results in drop-out after randomization.[7,20] These could be arguments for a multicenter stepped-wedge design of future studies instead of a randomized controlled setting.

Ongoing research and future perspectives

After literature search, 15 study protocols of ongoing research were identified on the topic. All authors were contacted to provide additional information on the publication and recruitment status and preliminary results. Three authors eventually provided some preliminary results on their research through conference abstracts, their main characteristics were summarized in the Tables 1–4.[25–27] Four study protocols that were published between 2011 and 2014 did not result in a full-text paper for unknown reasons. Currently, results of 8 studies on the topic are awaited, of which 5 of them are still recruiting. Three studies have currently completed or are nearing their inclusion. The first study, initiated by the University of Surrey, included 20 patients in a non-randomized setting to participate in a multimodal program (focusing on nutritional support and supervised exercise) 4 weeks prior to pancreatic surgery (ClinicalTrials.gov Identifier: NCT02940067). Second, a prospective trial, initiated by the University of Göteborg, randomized 245 patients between a multimodal prehabilitation program and early postoperative mobilization and standard care in patients undergoing pancreatic surgery (ClinicalTrials.gov Identifier: NCT03466593). A third study from the University of Besançon is currently investigating effects of interval training on outcomes in patients undergoing surgery for primary liver cancer, and are aiming to include 51 patients (ClinicalTrials.gov Identifier:NCT03518632).

This review stresses the need for continued research on the topic. Future research should focus on offering a multimodal approach (including physical exercise training, nutritional support, psychological support, smoking cessation interventions, and/or correction of exocrine and endocrine insufficiency) to high-risk patients specifically. Regarding physical exercise training, a home-based and highly personalized high-intensity training program with objective monitoring of progression could help to make it available and effective for those who need it the most. Telemonitoring and community-based training are specific opportunities in monitoring home-based training and increasing adherence. Furthermore, there is a need for standardized endpoints in evaluating the effect of prehabilitation. They should not only monitor the incidence of complications, but should also take their impact and consequences on quality of life into consideration. Currently, HPB surgery offers a specific window for prehabilitation, as a preparation phase is common, often biliary drainage has to be performed, and there is increasing evidence for neo-adjuvant treatment.[7,9,42]

Conclusion

Strong evidence on the clinical outcomes of prehabilitation programs in HPB surgery is lacking, mainly due to a large variation in the context and content of prehabilitation and used

outcome measures. However, a trend is seen towards less complications and a shorter hospital stay in the prehabilitation group.

Acknowledgements

The authors wish to thank Prof. Joost Klaase, Dr. Declan Dunne and Dr. Jason George for their advice about ongoing research and the provision of preliminary results.

Funding

The authors report no specific funds or grants for this study.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2021.04.021.

