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Personalised multimodal prehabilitation in cancer

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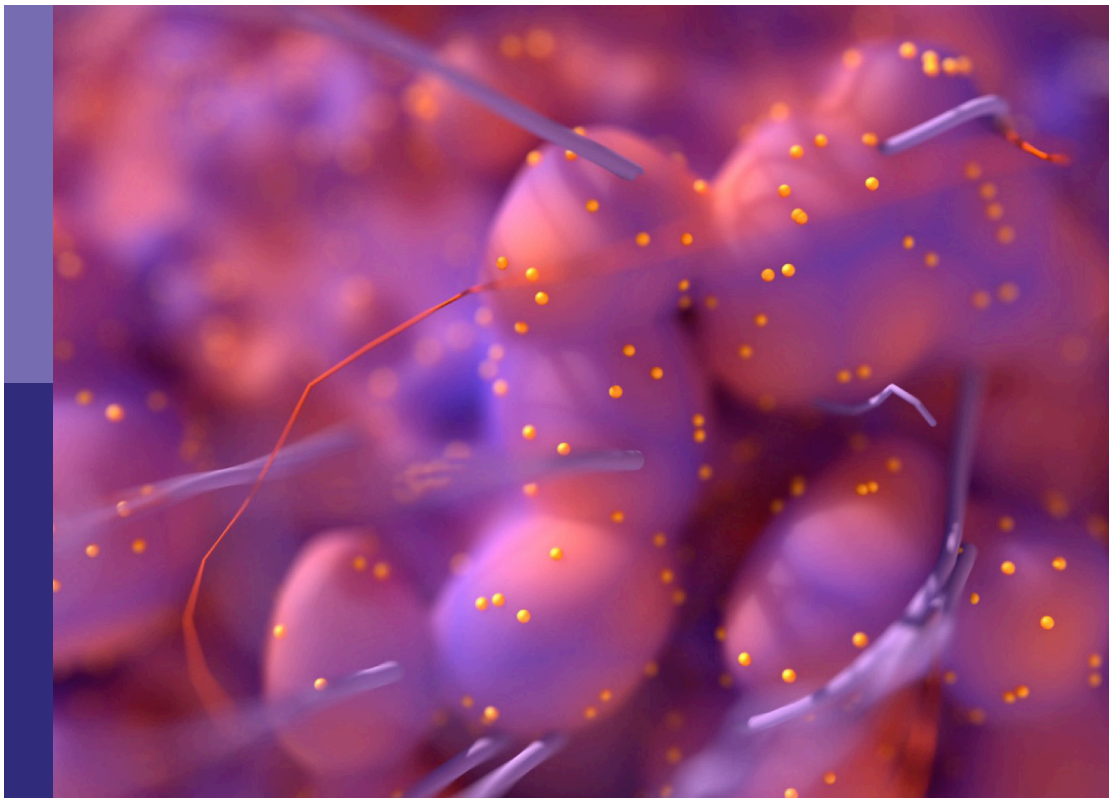

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Personalised multimodal prehabilitation in cancer

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Editorial: Personalised multimodal prehabilitation in cancer

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Editorial on the Research Topic
Personalised multimodal prehabilitation in cancer

Multimodality prehabilitation is a complex intervention that can enhance fitness, nutrition, and psychological resilience, with emerging evidence showing an improvement in perioperative and oncological outcomes (1). Personalised prehabilitation also has the potential to meet the widely adopted triple aim of health care: improving individuals' experience of care, improving population health, and providing value for money to the taxpayer (2). The contemporary prehabilitation model has adopted a multimodal approach, which attempts to address complex needs in patients having complex treatment pathways. Multimodal prehabilitation incorporates intervention components specifically selected for their potential synergistic effects on health outcomes. Prehabilitation enables people with cancer prepare for treatment through promoting healthy behaviours and through needs-based prescribing of exercise, nutrition, and psychological interventions, aiming to empower patients to maximise resilience to treatment and improve long-term health outcomes (3). In this Research Topic entitled *'Personalised Multimodal Prehabilitation in Cancer'* a collection of articles demonstrate how prehabilitation is now regarded as an integral part of a continuum spanning from cancer diagnosis to rehabilitation.

Multimodal prehabilitation interventions are often comprised of two or more of the following: i) aerobic and resistance training to attenuate cardiorespiratory and musculoskeletal deconditioning, ii) dietary interventions to counteract disease and/or treatment-related malnutrition, support anabolism and the metabolic cost of exercise; iii) psychological interventions to reduce stress, anxiety and associated morbidity; iv) the cessation of adverse health behaviours; and v) behavioural modification to support intervention initiation and adherence in the perioperative setting, whilst establishing self-management skills for long-term health behaviour change. In the perioperative setting,

prehabilitation interventions are often combined with medical optimization of comorbidities (e.g., assessing/treating anaemia, diabetes and medication corrections) through collaboration with specialists expert in the management of long-term conditions

Santa Mina et al. set the scene by introducing the concept of multiphasic prehabilitation across the cancer continuum. Multiphasic prehabilitation is an innovative paradigm shift away from reactive assessments, that happen too late in the patient cancer pathway to be of any use in preparing or optimising patients for major surgery or cancer treatment, towards proactive early intervention. Multiphasic prehabilitation is intended to provoke investigation of proactive interventions that focus on periods of relative health where the 'maximum tolerable dose' for a health intervention can be pursued more readily in the absence of active treatments that often erode fitness, appetite, mental health and motivation (Santa Mina et al.). Multiphasic prehabilitation is individualised through screening and targeted assessment. This requires nuance and tailoring to the existing and anticipated experiences at each phase of the cancer journey to minimize treatment-related side effects and subsequent treatment delays, thereby improving wellbeing and potentially improving long term outcomes. The 'aggressive' push for patient preparation in this setting, may be akin to training models of high-performance sport with cyclic rounds of training prior to competition, both with similar goals: to optimize health preceding an anticipated stressor, ensuring 'maximal performance' and rapid recovery.

Waterland et al. illustrate the growing prehabilitation literature base and recent clinical recommendations in their updated systematic review and meta analyses. Prehabilitation improved preoperative functional capacity and substantially reduced hospital length of stay, however they did not find a significant reduction in postoperative complications, 30-day readmissions or postoperative mortality. They emphasise various points for future research including, the assessment of prehabilitation cost effectiveness, the need for new technology to tailor interventions and outcome, and measurement standardisation across the literature to allow for more efficient data utilisation and cleaner meta-analyses that minimises research waste. Mao et al. provide an interesting updated systematic review and meta-analysis illustrating that pulmonary rehabilitation is a meaningful addition to the whole perioperative patient pathway and demonstrating its value in reducing post-operative pulmonary complications. This review lends its support to previous literature in the pulmonary rehabilitation field, where exercise prescription has always been an integral component.

Brahmbhatt et al. demonstrated an improvement in functional capacity using a multimodal exercise intervention composed of resistance and aerobic exercise. Although not inherently novel, this interventional study carefully documents participant experiences interrogating intervention design preferences, perceived benefits, behaviour change, prehabilitation as education and the ability of patients to regain control. Unanimously, participants spoke positively about multimodality prehabilitation with inclusion of dietetic and psychological support to manage emotional stress and optimise health, echoing the concept of multiphasic prehabilitation across the cancer continuum (4). Importantly, prehabilitation was shown as a catalyst for positive healthy behaviour change, engagement, adherence and enabling patients to regain control of their disease process and importantly their cancer journey. Grimmett et al. describe the evidence on patient experiences and attitudes towards prehabilitation, with a specific focus on how behaviour science could strengthen uptake and adherence in prehabilitation programmes in both research and clinical settings. They also identify how behaviour change techniques (BCTs) represent 'active ingredients' in boosting the success of prehabilitation strategies, using goal setting, graded tasks and self-monitoring, to promote longer-term behaviour change. This can also be a research endpoint, where behavioural scientists may set out to understand behaviour strategies to improve motivation and compliance with the exercise component of prehabilitation. Working alongside clinical colleagues, behavioural scientists are well-placed to employ intervention mapping processes, behavioural analysis, and patient-centred intervention development. They can also provide training to colleagues delivering the programs to ensure the identified BCTs embedded within it are employed appropriately. Grimmett et al. highlight the importance of including qualitative process evaluation in the design of new prehabilitation trials as it together with BCTs, are vital to the integrity of the multimodal prehabilitation intervention and maximise positives outcomes.

Gillis et al. through their scoping review show that current prehabilitation literature lacks standardised and valid nutritional assessment methods, often coupled with interventions that lack an evidence basis. They conclude that nutrition interventions were inconsistently applied and lack adherence to accepted nutritional guidance published in oncology or surgery. Large gaps in the evidence exist in adopting validated nutritional screening and malnutrition assessment methods, interrogation of the 'effect modification' of a single interventional treatment effect on outcomes independent of nutritional status, intervention monitoring, adherence, evaluation, and cancer cohort heterogeneity. Gillis et al. go a step further in describing the nutrition care process for perioperative patients advocating its adoption in surgical prehabilitation. Here they emphasise the importance of developing a core outcome and measurement dataset to effectively address these substantial research gaps in surgical prehabilitation studies, allowing data meta-analyses and reduce research waste.

The implementation of prehabilitation in real-world clinical practice is limited, mainly due to logistical large-scale deployment, patient access and economical sustainability. These limitations can be overcome by innovative use of technology to facilitate screening, assessment, remote monitoring, and true personalisation of interventions. Barberan-Garcia et al. discuss the challenges in digital innovation in surgical prehabilitation, highlighting real-

world issues and potential solutions e.g. digital physical activity prescription and behaviour change techniques aimed at improving perioperative outcomes. Digital technologies and remote monitoring is the future of true personalised prehabilitation.

We hope that this Research Topic presents a balanced view of the current challenges in cancer prehabilitation. We must move away from a 'one size fits all' approach and usher in a new era of individualised patient tailored multi-modal prehabilitation focussed on improving patient care and outcomes throughout the cancer journey.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Feasibility of Prehabilitation Prior to Breast Cancer Surgery: A Mixed-Methods Study

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Background: Breast cancer surgery results in numerous acute and long-term adverse outcomes; the degree to which these can be mitigated or prevented through prehabilitation is unknown.

Methods: We conducted a longitudinal, single-arm, mixed-methods study to examine the feasibility of prehabilitation in 22 women undergoing breast cancer surgery. All participants received an individualized exercise prescription including upper quadrant-specific resistance and mobility training and aerobic exercise for the duration of their surgical wait time. Feasibility was assessed by recruitment, adherence, attrition, and intervention-related adverse event rates. An exploratory investigation of intervention efficacy was conducted via a 6-min walk test, upper-quadrant strength and range of motion, volumetric chances associated with lymphedema, and participant-reported quality of life, fatigue, pain, and disability. Outcome assessments were conducted at baseline, prior to surgery, and at six and 12 weeks after surgery. Semi-structured interviews with a subset of participants (n = 5) and health-care providers (H; n = 2) were conducted to provide further insights about intervention feasibility. Qualitative data were analyzed using a hybrid inductive and deductive thematic analysis approach.

Results: Recruitment and attrition rates were 62 and 36%, respectively. Average prehabilitation duration was 31 days (range = 7–69 days). Seventy six percent of participants complied with at least 70% of their prehabilitation prescription. There was a clinically significant increase in the 6-min walk distance from baseline to the preoperative assessment (57 m, 95% CI = −7.52, 121.7). The interviews revealed that the intervention was favorably received by participants and HCPs and included suggestions that prehabilitation (i) should be offered to all surgical candidates, (ii) is an avenue to regain control in the preoperative period, (iii) is a facilitator of postoperative recovery, and (iv) is an opportunity to provide education regarding postoperative rehabilitation protocols. A preference for multimodal prehabilitation (including dietetic and psychological counseling) was also highlighted.

Conclusion: Our findings suggest that surgical prehabilitation in women with breast cancer is feasible. Data are hampered by study sample size and lack of a control group. Thus, randomized controlled trials to examine prehabilitation efficacy in people with breast cancer, especially interventions employing a multimodal strategy, are warranted.

Keywords: prehabilitation, breast cancer, survivorship, rehabilitation, oncology, surgery

INTRODUCTION

Breast cancer is the most common malignancy and principal cancer-related cause of death in adult females in industrialized nations (1). Surgery is a cornerstone of therapy and is indicated in more than 90% of people with breast cancer at some point during treatment (2). While highly effective at disease control, it often results in physical and psychosocial sequelae that significantly impair quality of life and may last for months or years after treatment completion (3, 4). For example, common regional postoperative effects include lymphedema, pain, axillary web syndrome, and upper-quadrant dysfunction, which manifests as a loss of strength and range of motion in chest, shoulder, arm, and cervical spine (5–8). Furthermore, whole-body adverse effects such as fatigue, which is disproportionately higher in people with breast cancer compared to other cancer populations, (9, 10) is reported by up to 95% of all patients during therapy (9). The severity of these symptoms, however, varies depending on a number of factors, including age, comorbid conditions, treatment regimen, and baseline physical well-being (11, 12). Higher levels of preoperative aerobic fitness are associated with better surgical outcomes including decreased postoperative complications and mortality in other clinical (13) and cancer populations (14–16). Although the relationship between objectively measured physical fitness and surgical outcomes in individuals with breast cancer has not been elucidated, higher physical activity levels are associated with earlier postoperative recovery (17). Taken together, this evidence suggests that physical fitness is a modifiable risk factor that may be targeted to improve surgical outcomes.

A burgeoning body of research is investigating the utility of preoperative interventions, known as prehabilitation, to optimize posttreatment health outcomes. Numerous reviews of the prehabilitation literature in cancer populations demonstrate several important benefits, including improved preoperative and postoperative physical function, reduced hospital length of stay, and fewer postoperative complications (18–24). However, this literature exists almost exclusively in people undergoing tumor resection for thoracoabdominal malignancies, with breast cancer prehabilitation remaining largely unexamined. In the only breast cancer surgery prehabilitation study to date, Baima and colleagues (25) found that teaching preoperative shoulder stretches for individuals undergoing breast cancer surgery was feasible via in-person or by video with similar postoperative outcomes across groups. The feasibility and effects of prehabilitation targeted at improving broader markers of quality of life and symptom burden, such as fitness, fatigue, and pain before and after surgery, are otherwise unknown. As a preliminary step at furthering this field of research, we sought to assess the feasibility and acceptability of an individualized, home-based prehabilitation intervention prior to breast cancer surgery using a mixed-methods approach. The secondary objective was to explore the potential benefit of prehabilitation on physical fitness and participant-reported physical and psychosocial well-being over time to inform future studies with point estimates and variability data.

MATERIALS AND METHODS

Study Design

This study was a prospective, single-arm, feasibility study with an emergent, embedded mixed-methods design. Qualitative methodology was implemented part-way through the study to further understand the participants' experience with prehabilitation and their preferences regarding intervention design. This study was approved by the University Health Network Research Ethics Board (#16-6165), and all participants provided written informed consent prior to initiating any study activity.

Sampling and Eligibility

A convenience sample of people undergoing breast cancer surgery was recruited from breast cancer clinics at the Princess Margaret Cancer Centre. Participants were eligible if they (i) were diagnosed with stage I–III breast cancer; (ii) consented to surgery (mastectomy or lumpectomy); (iii) had a surgical waiting period of at least 3 weeks; (iv) were proficient in English; or (v) were between the ages of 18 and 80 years. Patients were excluded from the trial if they (i) received or were receiving neoadjuvant treatment; (ii) had medical contraindications to exercise; or (iii) had active shoulder pathology. Qualitative interview participants were recruited via convenience sampling from the quantitative strand (i.e., individuals who had participated in prehabilitation). In addition to conducting semi-structured interviews among patient-participants, we recruited health-care practitioners (HCPs) from the breast cancer clinic via convenience sampling to provide their perceptions regarding the feasibility and value of prehabilitation for people with breast cancer.

Intervention

The prehabilitation intervention comprised of individually tailored, home-based exercise prescriptions commencing immediately following the baseline assessment and until the day of surgery. The exercise prescriptions were developed and delivered by a Registered Kinesiologist (RKin) and consisted of aerobic exercise 3 to 5 days per week for 30–40 min per session,

and upper quadrant-specific resistance training 2 to 3 days per week. Aerobic exercise prescriptions typically included brisk walking at an intensity of four to six on a 10-point rating of perceived exertion (RPE) scale (26). Upper quadrant-specific resistance training consisted of two to three sets of 10 to 12 repetitions per exercise, with each session incorporating up to eight exercises (standing rows, shoulder external rotation, front raise, lateral raise, bicep curls, triceps extensions, wall push-ups, and chest press). Training progression per modality was guided by the RKin and occurred when the participant could complete the aerobic exercise with mild exertion (RPE of 0–3) or when the participant could complete 15 repetitions of any of the resistance exercises without eliciting at least moderate exertion (3–6) on the RPE scale. The intervention also included stretching and mobility exercises which reflected standard postoperative rehabilitation. This allowed participants to familiarize themselves with postoperative protocols while functionally unimpaired.

All participants were provided with resistance bands and an exercise manual to facilitate home-based exercise. The RKin communicated with the participants on a weekly basis via phone calls or emails to support program compliance and appropriate progression and to address any barriers to exercise (including questions about appropriate exercise completion) that may have prevented ongoing participation.

Outcomes

Demographic, disease, and treatment-related data were collected at baseline from the participant and by chart review. Measures of intervention efficacy were collected at baseline, approximately 1 week prior to surgery and at 6 and 12 weeks postoperatively. Qualitative interviews with patient-participants were conducted at the last study assessment or shortly thereafter. Qualitative interviews with HCPs were conducted after all participants had completed the intervention.

Quantitative Feasibility Outcomes

The recruitment rate was calculated as the number of participants successfully consented over the total number of patients approached. Intervention adherence was captured through participant self-report via exercise logs. Adherence to resistance training was calculated as the volume of exercise repetitions completed relative to the lower end of the range of repetitions prescribed. Adherence to the aerobic exercise was defined as total quantity completed per week relative to the lower end of the range prescribed. Attrition was assessed as the number of participant-withdrawals relative to the participants who consented and was reported per assessment timepoint. Reasons for participant withdrawal were also collected. Intervention-related adverse event information was collected from the participants during weekly communication with the RKin. Lastly, participant satisfaction was collected at the last study assessment via a study-specific satisfaction questionnaire.

A priori, we determined that feasibility would be confirmed with (i) a recruitment rate $>60\%$; (ii) $>70\%$ intervention adherence; (iii) attrition rate $<30\%$; and (iv) no serious adverse events [defined as anything above a Grade 2 of the CTCAE v5 (27)] related to participation in the prehabilitation intervention. Participant satisfaction was captured through a satisfaction survey to understand the participant's experience with the intervention.

Quantitative Exploratory Outcomes

Aerobic functional capacity was measured using the 6-min walk test (6MWT) (28). Upper-extremity strength was measured via handgrip dynamometry (Jamar®, Chicago, IL, United States) and manual muscle testing using a digital handheld dynamometer (MicroFET2; Hoggan Scientific®, Salt Lake City, UT, United States) for elbow flexion and extension, and shoulder abduction, flexion, and extension. An active range of motion of the glenohumeral and scapulothoracic joints was measured via goniometry for the following actions: shoulder flexion, extension, internal and external rotation, and abduction. Other measurements included waist circumference (WC), body mass index (BMI), lean body mass, body fat percentage (BF%), and fat mass. Upper-extremity limb size to detect potential development of lymphedema was measured via circumferential measurements at (i) the metacarpophalangeal joints; (ii) the wrist; (iii) 10 cm distal to the lateral epicondyles; and (iv) 15 cm proximal to the lateral epicondyles (29).

Participant-reported upper-quadrant function was collected using the disabilities of the arm, shoulder and hand (DASH) questionnaire. The brief pain inventory (BPI) was used to collect cancer-specific pain (30). Fatigue was assessed using the fatigue subscale of the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) questionnaire (31). Health-related quality of life (HRQOL) was measured using the second version of the 36-Item Short Form Health Survey (SF-36 v2) (32). The Godin–Shephard Leisure Time Exercise Questionnaire-Leisure Score Index (GLTEQ-LSI) was used to measure physical activity levels (33, 34). Lastly, global level of functioning and disability were measured using the 36-item World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) (35).

Qualitative Assessment of Feasibility and Participant Experience

The purpose of the participant interviews was to understand their experience with prehabilitation and different factors that affected feasibility of the intervention (e.g., challenges to participation and preferences regarding the exercise prescription and intervention delivery). We sought to interview all participants to understand the variability in individual experiences because of the different life stages and physical activity backgrounds of the participants. To further understand intervention design and viability, as well as the perceived value of prehabilitation, we also interviewed HCPs within the breast cancer clinic. All interviews were semi-structured and included open-ended questions along with relevant prompts. The interview guide was pilot tested to allow the interviewer to ensure familiarity with the script. All interviews were conducted either in-person or over the telephone by

the RKin, were recorded, and were transcribed verbatim prior to analysis.

Data Analysis

Quantitative Data

Participant demographics and clinical characteristics were analyzed using descriptive statistics [mean ± standard deviation, and frequency (%)]. Participation rates, reasons for exclusion and dropout, and attrition rates were analyzed by reason frequency and percentages as appropriate. Adherence to the prehabilitation prescription was expressed as a percentage of exercise completed relative to the minimum training volume prescribed for both aerobic and resistance training. Participants were also categorized as adherent (completed >70% of their exercise prescription in each session), partially adherent (completed <70% of their exercise prescription in some sessions), or non-adherent (completed <70% of their prescription in all sessions). Descriptive statistics were also used to analyze the frequency of responses in the participation satisfaction survey.

Exploratory outcomes were assessed using a linear mixed-effects model to assess changes over time. Models were fitted with the following variables as fixed effects: (i) Surgery type (categorized into either lumpectomy or mastectomy); (ii) Measurement timepoint; and (iii) Prehabilitation duration (in number of days). Individual participants were included as random effects. Comparisons between timepoints were made using Tukey HSD (honest significant differences) *post hoc* pairwise comparisons, and data were analyzed under the intention-to-treat principle. Missing data values were accounted for using maximum likelihood estimation (with the assumption that data are missing at random) in the model. All analyses were done in R version 3.4.1.

Qualitative Data

Interview data were analyzed using Braun and Clarke's six-step approach for thematic analysis in a hybrid deductive and inductive manner (36, 37). A deductive analysis approach allowed for a detailed examination of themes directly related to the interview questions. For data that emerged during the interview but was not planned or directly related to the interview questions, we used an inductive analysis approach. This approach is data-driven and allows for the development codes and themes based on the content of the data, rather than trying to strictly fit the data into a preexisting framework or theory (36). Interview transcripts were read multiple times by the first author, and emerging concepts were identified via memoing. Codes were then categorized into themes. Descriptions of the themes were created, and representative quotes were chosen and reviewed by the last author.

Integration of Quantitative and Qualitative Data

There were multiple points of quantitative and qualitative integration in this study. Integration at the methods level was achieved through the sampling frame where participants for the qualitative portion were recruited from those who had participated in the quantitative portion (38). Mixing of the methods also occurred at the interpretation and reporting phase, where quantitative and qualitative data are integrated using a narrative weaving approach and reported together on a theme-by-theme basis (38).

RESULTS

Quantitative Feasibility Findings

The study flow diagram is presented in **Figure 1**, and participant demographics are in **Table 1**. From April 2017 to July 2018, 45 eligible patients were approached in clinic, of whom 28 (62%) consented to participate in the study. Primary reasons for declining participation were travel/distance-related concerns (n = 3), too much anxiety to commit to prehabilitation (n = 2), and lack of interest in exercise/research participation (n = 5). Five patients did not provide a reason for declining participation. Twenty-two (n = 22) participants attended the baseline assessment and received the intervention. Reasons for dropout between study consent and the baseline assessment included change in treatment plan resulting in ineligibility (n = 1) and withdrawal from the study due to time constraints (n = 1). The study team was unable to contact four participants to book study visits. Study enrollment rate, calculated as number of participants who received the intervention relative to the number approached, was approximately 49%. The overall attrition rate from baseline to the last study assessment was approximately 36% (n = 8). The average prehabilitation window (i.e., the period from the baseline to preoperative assessment) was approximately 30 ± 16.59 days. The surgical wait time for individuals in this study (i.e., the date from treatment decision to the date of surgery) was 38 ± 16.56 days. There were no intervention-related adverse events during the study.

Five (23%) participants did not submit their exercise logs for adherence analysis. On average, adherence to the minimum range of the aerobic exercise prescription was 142.22 ± 82.66% and adherence to the resistance training prescription was 114.44 ± 38.26%. Adherence levels exceeded 100% because most participants were exercising beyond the lower end of their exercise prescription range. Of the 17 participants that provided adherence data, 13 (76%) were considered adherent to their prescription (i.e., completed >70% of exercise volume prescribed for each session). Two participants partially adhered to their prescription (i.e., completed <70% of their prescribed exercise volume in some sessions), and two participants were non-adherent (i.e., completed <70% of their prescribed exercise volume in all the sessions).

Eleven participants completed the participant satisfaction survey at the final study assessment. Of those, all 11 (100%) reported that they experienced benefits from participating in the study, had no side effects or harm related to the study, and did not consider discontinuing participation. Ten (90.9%) found the exercise manual helpful, and eight (72.7%) said they were able to complete all the exercises prescribed to them. On average, participants rated the program 8.6 out of a score of 10, with 0 being the lowest and 10 being the highest score possible. All respondents indicated that they planned to continue exercising

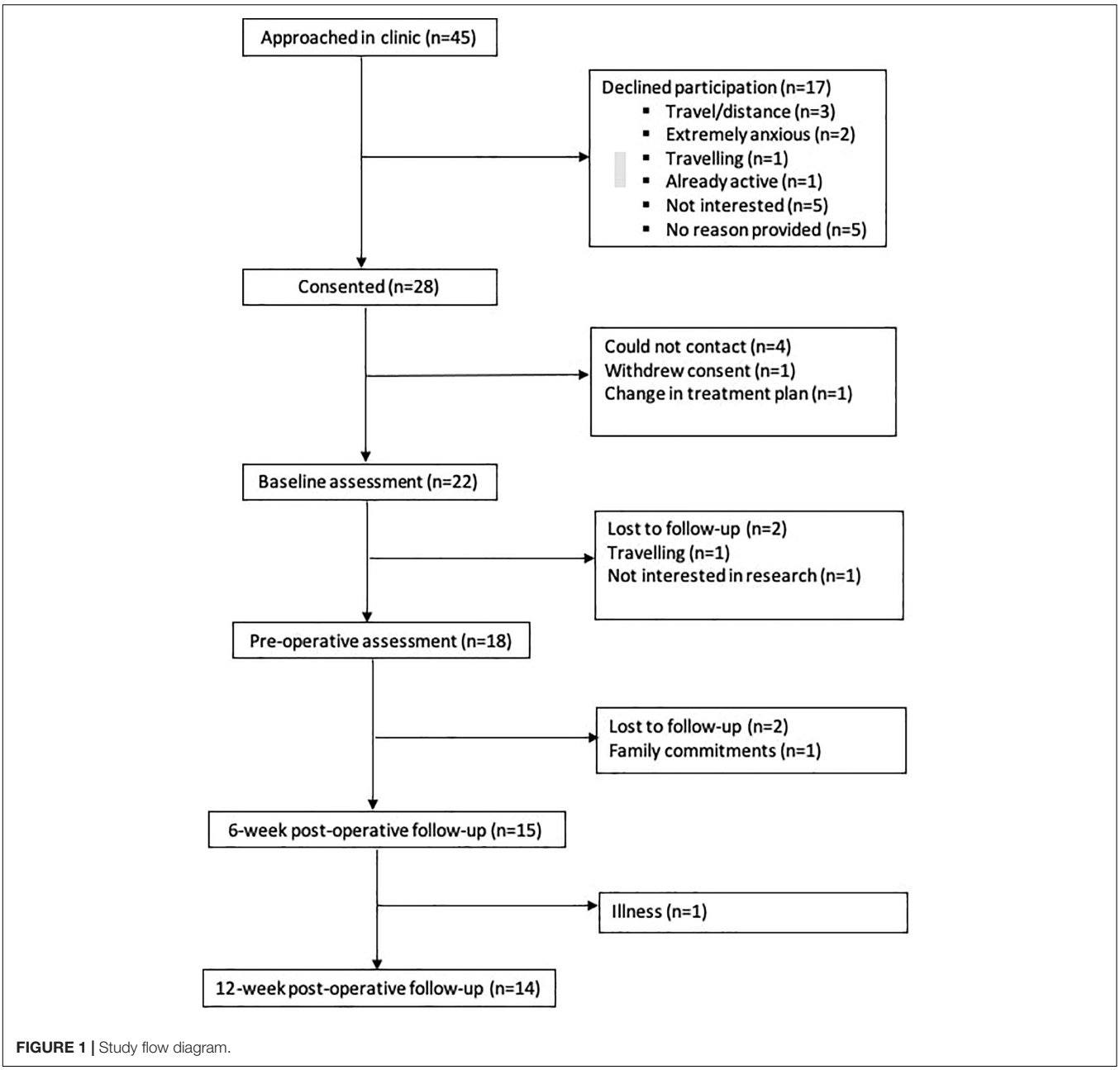

FIGURE 1 | Study flow diagram.

on a regular basis (45–60 min per day, 3–4 days per week), would recommend the program to anyone else undergoing surgery, and believed that prehabilitation helped them recover after surgery.

Quantitative Exploratory Findings

Mean scores for objectively measured outcomes of physical fitness and participant-reported outcome measures are presented in **Tables 2**, **3**, respectively. Between-timepoint differences for physical fitness and participant-reported outcomes have been reported in **Supplementary Tables 1**, **2**. Because the primary purpose of this study was not to assess intervention efficacy, the sample was underpowered to detect statistically significant differences in exploratory outcomes. As such, we have highlighted outcomes, which demonstrated clinically meaningful changes.

The 6-min walk distance increased from baseline to the preoperative assessment by 57.10 ± 24.0 m (95% CI = −7.52, 121.7). While there was a small decrease in 6MWT distance from the preoperative assessment to the 6-week postoperative assessment (−5.51 ± 27.6 m [−79.74, 68.7]), scores remained greater than at baseline. There was an overall increase in 6MWT distance of 62.90 ± 24.00 m (−1.81, 127.60) from baseline to the last study assessment. Although a minimal clinically important difference (MCID) has not been established in the breast cancer setting, in other cancer populations it has been identified to be around 20 m (39). The overall 6MWT distance change represents

almost three times the MCID. All other physical fitness outcomes remained relatively stable over the study period.

An increase in DASH scores of 16.18 ± 4.96 (2.74, 29.63) points was observed between the preoperative and 6-week postoperative assessment, indicating a clinically important increase in upper-quadrant disability (MCID of 15 points) (40).

TABLE 1 | Participant baseline characteristics (n = 22).

Characteristic	Mean ± SD
Age	54.18 (±10.98)
	Frequency (%)
Ethnicity	
White/Caucasian	14 (63.64)
Latino/Hispanic	2 (9.09)
East Asian	2 (9.09)
South East Asian	1 (0.05)
South Asian	1 (4.55)
Ashkenazi Jewish	1 (4.55)
Prefer not to answer	1 (4.55)
Marital status	
Married	12 (54.55)
Divorced	2 (9.09)
Single	2 (9.09)
Common-law	2 (9.09)
Widowed	1 (4.55)
Other	2 (9.09)
Prefer not to answer	1 (4.55)
Education	
Finished University/college	15 (68.18)
Some University/college	3 (13.64)
Some high school	1 (4.55)
Other	2 (9.09)
Prefer not to answer	1 (4.55)
Working status	
Working/studying full-time	11 (50.00)
Working/studying part-time	2 (9.09)
Retired	2 (9.09)
Unemployed	1 (4.55)
Disability/sick leave	2 (9.09)
Other	3 (13.64)
Prefer not to answer	1 (4.55)
Socioeconomic status	
>$75,000	9 (40.91)
$40,000–$75,000	2 (9.09)
$20,000–$39,000	2 (9.09)
<$20,000	3 (13.64)
Prefer not to answer	6 (27.27)
Surgery type	
Unilateral lumpectomy with SLNB	12 (54.55)
Unilateral mastectomy with SLNB	2 (9.09)
Unilateral mastectomy with ALND	1 (4.55)
Bilateral mastectomy with SLNB	4 (18.18)
Bilateral mastectomy with SLNB and insertion of tissue expanders	1 (4.55)
Bilateral mastectomy with immediate autologous reconstruction	1 (4.55)

From baseline to the 12-week postoperative assessment, there was an overall worsening in fatigue levels demonstrated by a reduction of 4.63 ± 3.34 (−13.7, 4.41) points in FACT-F scores which have an MCID of three points (41). The physical component score of the SF-36 questionnaire consistently worsened over the study period with a decrease of 5.90 ± 2.17 (−11.75, −0.05) points from the first to the last assessment. The mental component score, on the other hand, worsened from baseline to the preoperative assessment but then improved by 4.36 ± 2.25 (−1.72, 10.44) points from the pre- to 6-week postoperative assessment. The MCID for SF-36 scores is between 3 and 5 points in various clinical populations (42). Lastly, GLTEQ-LSI scores increased over the study period from 22.8 ± 5.30 at baseline to 33.8 ± 6.12 at the last study assessment, which reflects a change from being insufficiently active at baseline according to physical activity guidelines for cancer survivors to being sufficiently active at 12 weeks after surgery (43, 44).

Qualitative Findings

Five participants and two HCPs who are both clinical nurse coordinators volunteered to participate in the interviews. A total of eight themes emerged, which were then grouped into two distinct categories (intervention feasibility and participant experience) described below. Representative quotes for each theme are provided in **Table 4**.

Intervention Feasibility

Elements related to feasibility of the intervention were coded and categorized into the following three themes: (i) Appropriateness of the intervention, (ii) Barriers and facilitators to participation, and (iii) Target population.

The appropriateness of the intervention was discussed by the women. Participants described the prehabilitation intervention as convenient because the prescription is entirely bodyweight- and resistance band-based. Some participants traveled during the preoperative period and were able to continue exercising because of the portability of the resistance bands. Further, participants described the intervention as easy to follow; individualization of the prescription allowed each participant to receive a program that they were able to follow with ease regardless of previous physical activity experience.

While the intervention was deemed appropriate, there were both barriers and facilitators to participation. It was evident through the interviews that both participants and HCPs recognized that there might be challenges to optimal uptake of the intervention. Potential barriers that emerged were related to motivation and the weather. Lack of time was another important barrier that was commonly referred to by participants because the preoperative period is typically occupied with many medical appointments and personal/professional responsibilities. While those were the only barriers mentioned, a couple of characteristics of the intervention design surfaced as potential facilitators of exercise intervention adherence. Participants reported that the in-person instruction of the exercises, which allowed them to practice and receive feedback, was especially helpful and increased how comfortable participants felt with being able to exercise on their own at home. Moreover, the

TABLE 2 | Mean estimates ± SE (95% CI) for objectively measured physical fitness outcomes (n = 22).

Outcome	Baseline	Preoperative	6-week postoperative assessment	12-week postoperative assessment
6MWT (m)	474 ± 19.9 (433, 514)	531 ± 22.6 (485, 576)	525 ± 24.2 (476, 574)	536 ± 22.6 (491, 582)
Weight (kg)	77.5 ± 3.23 (70.7, 84.4)	77.7 ± 3.24 (70.8, 84.6)	77.5 ± 3.25 (70.6, 84.4)	77.9 ± 3.24 (71.0, 84.8)
Waist circumference (cm)	94.7 ± 2.22 (90.0, 99.4)	96.6 ± 2.28 (91.8, 101.4)	96.5 ± 2.35 (91.6, 101.4)	97.7 ± 2.30 (92.9, 102.5)
Body fat (%)	38.0 ± 1.73 (34.4, 41.6)	38.0 ± 1.83 (34.2, 41.8)	37.6 ± 1.94 (33.6, 41.6)	36.4 ± 1.86 (32.6, 40.2)
BMI (kg/m^2)	29.7 ± 1.26 (27.1, 32.4)	29.7 ± 1.27 (27.1, 32.4)	29.6 ± 1.27 (26.9, 32.2)	29.8 ± 1.27 (27.1, 32.5)
Hand grip strength (kg)	51.6 ± 3.17 (45.1, 58.1)	51 ± 3.41 (44.0, 57.9)	50.0 ± 3.69 (42.5, 57.4)	52.8 ± 5.50 (45.7, 59.9)
Upper-extremity strength (kg)				
Elbow flexion	22.5 ± 1.28	22.8 ± 1.34	20.69 ± 1.60	20.9 ± 1.43
Elbow extension	22.2 ± 1.38	21.6 ± 1.43	19.9 ± 1.62	19.5 ± 1.49
Shoulder flexion	18.3 ± 0.94	18.1 ± 1.02	17.2 ± 1.30	17.8 ± 1.09
Shoulder extension	25.6 ± 1.75	27.2 ± 1.84	26.5 ± 2.38	24.8 ± 1.98
Shoulder abduction	16.7 ± 0.92	16.8 ± 1.01	15.2 ± 1.36	15.7 ± 1.10
Shoulder range of motion (°)				
Right flexion	161 ± 3.98 (153, 169)	165 ± 4.38 (156, 174)	141 ± 4.82 (131, 151)	149 ± 4.52 (140, 158)
Right extension	60.2 ± 3.43 (53.1, 67.3)	61.6 ± 3.56 (54.3, 68.9)	56.0 ± 3.76 (48.3, 63.7)	61.3 ± 3.63 (53.8, 68.8)
Right abduction	160 ± 4.99 (150, 170)	167 ± 5.52 (156, 178)	147 ± 6.11 (135, 159)	156 ± 5.70 (145, 168)
Right internal Rotation	46.6 ± 3.34 (39.8, 53.4)	53.6 ± 3.83 (45.9, 61.3)	45.0 ± 4.32 (36.3, 53.7)	52.5 ± 4.14 (44.2, 60.9)
Right external rotation	97.3 ± 4.46 (88.0, 107.0)	100.3 ± 4.81 (90.4, 110.0)	93.9 ± 5.16 (83.4, 104.0)	90.7 ± 4.91 (80.7, 101.0)
Left flexion	163 ± 4.00 (155, 172)	163 ± 4.28 (155, 172)	158 ± 4.47 (149, 167)	161 ± 4.30 (152, 170)
Left extension	56.5 ± 3.43 (49.4, 63.5)	57.5 ± 3.65 (50.0, 65.0)	57.8 ± 3.83 (50.0, 65.5)	60.2 ± 3.66 (52.7, 67.7)
Left abduction	163 ± 4.52 (154, 173)	163 ± 4.84 (153, 173)	159 ± 5.05 (149, 170)	165 ± 4.85 (155, 175)
Left internal rotation	46.9 ± 3.62 (39.4, 54.3)	51.5 ± 3.97 (43.5, 59.6)	43.8 ± 4.19 (35.3, 52.3)	54.5 ± 3.98 (46.4, 62.6)
Left external rotation	91.0 ± 6.20 (77.9, 104.2)	93.5 ± 6.34 (80.2, 106.8)	89.0 ± 6.42 (75.6, 102.5)	85.2 ± 6.34 (71.8, 98.5)
Lymphedema (cm)				
Right MCP joints	20.1 ± 0.29 (19.5, 20.7)	19.6 ± 0.30 (19.0, 20.2)	19.7 ± 0.31 (19.1, 20.4)	19.6 ± 0.30 (19.0, 20.3)
Right wrist	16.6 ± 0.27 (16.0, 17.1)	16.4 ± 0.28 (15.8, 16.9)	16.5 ± 0.29 (15.9, 17.1)	16.5 ± 0.28 (15.9, 17.0)
Right 10 cm distal to lateral epicondyles	25.2 ± 0.57 (24.0, 26.4)	25.2 ± 0.58 (24.0, 26.4)	25.2 ± 0.59 (24.0, 26.4)	25.0 ± 0.58 (23.8, 26.2)
Right 15 cm proximal from lateral epicondyles	33.8 ± 1.04 (31.6, 36.0)	33.1 ± 1.07 (30.9, 35.3)	33.3 ± 1.08 (31.1, 35.6)	33.5 ± 1.07 (31.3, 35.7)
Left MCP joints	19.6 ± 0.27 (19.0, 20.2)	19.7 ± 0.28 (19.2, 20.3)	19.6 ± 0.29 (19.0, 20.2)	19.7 ± 0.28 (19.1, 20.3)
Left wrist	16.3 ± 0.23 (15.9, 16.8)	16.2 ± 0.24 (15.7, 16.7)	16.2 ± 0.24 (15.7, 16.7)	16.4 ± 0.24 (15.9, 16.9)
Left 10 cm distal to lateral epicondyles	25.1 ± 0.54 (23.9, 26.2)	24.9 ± 0.55 (23.7, 26.1)	25.2 ± 0.56 (24.0, 26.4)	25.0 ± 0.55 (23.8, 26.1)
Left 15 cm proximal from lateral epicondyles	33.4 ± 1.02 (31.1, 35.5)	33.0 ± 1.04 (30.8, 35.1)	32.9 ± 1.05 (30.7, 35.1)	33.1 ± 1.04 (30.9, 35.3)

6MWT, 6-min walk test; MCP, metacarpophalangeal; Hand grip strength and upper-extremity strength values are reported as a sum of both sides.

weekly phone conversations along with the exercise logs, which were given to participants to track adherence, also appeared to be important facilitators to exercise adherence. Participants said that they created a sense of accountability, which was further augmented by the structure of the exercise prescription.

Based on the discussions pertaining to the intervention, it was recognized that not all patients would be willing to participate in prehabilitation; generally, both the participants and the HCPs suggested that prehabilitation should be made available to everyone receiving surgery.

Participant Experiences

Concepts related to the participants' experiences with prehabilitation were collated into the following themes: (i) Intervention design preferences; (ii) Perceived benefit; (iii) Health behavior change; (iv) Regaining control; and (v) Prehabilitation as education.

Participants shared their preferences regarding the prehabilitation intervention including what they enjoyed and what they would have liked to see as part of the study. These preferences were further described and organized into the subthemes of (i) "multimodal care" which explains the need to include other complementary modalities of health behavior change in the prehabilitation intervention and (ii) "the need for an exercise professional" which highlights the need for an exercise professional to be delivering prehabilitation and rehabilitation-related programming. Firstly, participants almost unanimously spoke about the need to include either dietetic

TABLE 3 | Mean estimates ± SE (95% CI) for participant-reported outcomes (n = 22).

Outcome	Baseline	Preoperative	6-weeks postoperative assessment	12-weeks postoperative assessment
GLTEQ	22.8 ± 5.30 (11.91, 33.7)	37.9 ± 6.10 (25.53, 50.3)	21.7 ± 6.31 (8.92, 34.5)	33.8 ± 6.12 (21.38, 46.2)
WHODAS: Average Disability Score	30.0 ± 2.34 (25.1, 34.8)	29.2 ± 2.57 (23.9, 34.5)	33.2 ± 2.69 (27.7, 38.7)	30.2 ± 2.63 (24.8, 35.5)
FACT-F	37.9 ± 2.54 (32.7, 43.1)	39.7 ± 3.02 (33.6, 45.8)	36.0 ± 3.26 (29.4, 42.6)	33.3 ± 3.13 (26.9, 39.6)
BPI: Severity	1.63 ± 0.36 (0.89, 2.36)	2.03 ± 0.40 (1.21, 2.84)	1.72 ± 0.42 (0.86, 2.58)	1.82 ± 0.41 (0.98, 2.66)
BPI: Interference	1.33 ± 0.48 (0.34, 2.33)	1.48 ± 0.53 (0.39, 2.58)	2.18 ± 0.56 (1.04, 3.32)	1.54 ± 0.55 (0.42, 2.65)
DASH	8.99 ± 3.54 (1.73, 16.2)	11.97 ± 4.28 (3.31, 20.6)	28.16 ± 4.44 (19.19, 37.1)	20.96 ± 4.28 (12.28, 29.6)
SF-36: PCS	35.50 ± 1.46 (32.6, 38.5)	33.70 ± 1.79 (30.1, 37.4)	30.50 ± 1.95 (26.6, 34.5)	29.60 ± 1.86 (25.9, 33.4)
SF-36: MCS	43.00 ± 1.70 (39.5, 46.5)	41.20 ± 1.96 (37.2, 45.2)	45.60 ± 2.09 (41.3, 49.8)	44.90 ± 2.02 (40.8, 49.0)

GLTEQ, Godin Leisure Time Exercise Questionnaire; WHODAS, World Health Organization Disability Assessment Schedule; FACT-F, functional assessment of cancer therapy—fatigue; BPI, brief pain inventory; DASH, disabilities of arm, shoulder, and hand; SF-36 PCS, 36 item short form survey physical component score; SF-36 MCS, 36 item short form survey mental component score.

and/or a psychological support to help with stress and emotion management to optimize health in the preoperative period, while recognizing that there may be differing individual needs and preferences. Secondly, participants indicated that having an oncology-trained exercise professional was an asset that allowed them to feel more comfortable with their prehabilitation regimens. They recognized that having a trained professional would provide insight that might not be available if they were to seek out exercise support independently. Whether participants wanted consistent supervised training from the exercise professional was mixed. While some suggested that it might be helpful to have weekly sessions, others said that the home-based prescription was more appropriate given time constraints.

All the participants reported experiencing benefit from prehabilitation, including the perception that it facilitated earlier recovery and provided a positive distraction. In addition to the specific benefits from the intervention, many participants identified prehabilitation as a catalyst for positive health behavior changes. They reported that prehabilitation provided the momentum to make health behavior changes that they had been intending to make not just in the preoperative period but also in the postoperative period. Furthermore, many participants reported that prehabilitation allowed them to regain a sense of control during an otherwise tumultuous period where individuals often felt stripped of their autonomy. In this way, the loss of control that was frequently discussed as a result of frequent medical visits and impending treatment was partially addressed with a prehabilitation program.

Finally, the use of the prehabilitation intervention prior to surgery as a tool to educate patients also emerged as an aspect of the intervention that participants found to be helpful. It allowed participants the opportunity to ask questions that may not have the chance to ask their oncologists/nurses given the time constraints during their medical appointments and to learn about what they *should* be doing rather than what they *should not*.

DISCUSSION

Our primary objective was to assess the feasibility and acceptability of a home-based prehabilitation intervention prior to breast cancer surgery. We were able to recruit 28 patients out of the 45 that were approached (62%), slightly surpassing our anticipated recruitment rate of 60% to indicate feasibility for future studies. Study enrollment rate was approximately 49%. However, the attrition rate at the last study timepoint was 36% which was higher than the pre-decided threshold for success (30% overall attrition). Reasons for dropout included illness, other time commitments, and travel. These have previously been cited in the literature as barriers to participation in clinical trials, including exercise studies (45–47). The perioperative period may be especially susceptible to attrition given the substantial burden associated with medical visits at that time. The attrition rate in this study was slightly higher than the 25% reported by Baima and colleagues in their breast cancer surgical prehabilitation study (25). The difference in attrition rates between the two studies may be attributed to the fact that Baima and colleagues collected data at the follow-up oncology appointments and did not require additional center visits. Extra hospital visits, as well as illness and treatment-related mood disturbances, have previously been cited as a reason for dropout from clinical trials (45–48).

Overall adherence to the intervention in this study was impressive, with most participants exercising more than they were prescribed (approximately 142 and 114% for aerobic and resistance exercise, respectively), with over 75% of participants of those who provided data adhering fully to their prescription. There were no adverse events related to the intervention. Collectively, these results suggest that the exercise intervention that was used in this study is both safe and feasible for this population. This is unsurprising given that patients are typically asymptomatic and are not functionally limited prior to surgery compared to the acute postoperative/adjuvant treatment period. In fact, the preoperative window may be when patients are at their healthiest during their treatment course. Qualitative findings were congruent with the quantitative adherence data. Only a few participants reported experiencing any barriers to participation (e.g., weather, motivation, and time) but usually would find an alternative exercise modality, which would allow them to adhere to their prescription. Instead, participants found that elements of the program (e.g., a home-based setting, using resistance bands, having to report adherence) facilitated adherence to the protocol, which explains the high adherence rates. Baima and

TABLE 4 | Selected quotes from participant and health care provider interviews.

Theme Subtheme	Representative quote(s)
Intervention Feasibility	
Appropriateness of the intervention	"So I followed the exercises [prescribed as part of the prehabilitation intervention] in addition to the ones I was already going to do and I mean they were easy exercises. . .anyone could have done them, which made it really great for any women of any age at any physical level." [ID01]
	"Those [resistance bands] were fun! I've never used them before, and they were easy to use. I actually went away for a few days during the period before the surgery and it was great because I could stick them in a suitcase." [ID28]
Barriers and facilitators to participation	***Barriers:*** "Weather would dictate walking. I was doing some rebounding back then as well, so there were no barriers there in my house. . .so other than weather for getting outside, nothing." [ID20] ***Facilitators:*** "What I found most helpful was doing a run through with you of them [exercises] the first time out, making sure you're doing them correctly." [ID24] "That checklist [exercise log] recommended how many times a week to do each activity and it gave me that motivation to check that off and I brought that back to you. It held me accountable to keep doing the exercise. . ." [ID16]
Target population	"I actually have said to many nurses and doctors after that it [prehabilitation] should be something that is mandatory and should be implemented at the hospital for every person going through the surgery." [ID24]
	"I think it's valuable for everyone. I just think it's such an overwhelming time for patients, so when we present it as an option, I totally get why some women aren't interested but I think if you present it as this valuable resource, it's going to be really helpful for you recovery." [HCP1]
Participants' Experiences	
Intervention design preferences	
Multimodal care	"Those things [diet, psychological wellbeing] do go hand-in-hand. You know, the diet and exercise are key things around making a successful recovery, so if there was a way to engage that. . .that might be helpful to other patients as well." [ID24]
Need for an exercise professional	"When you're having very specific surgery, where someone is actually familiar with it, it's not like I can call up a physio center and say, 'oh can you help me because these problems.' You need to have someone who specializes and recognizes what the issues are. . ." [ID24].
	"I think it would be a good idea to do it [exercise training] in person maybe, but I'm not sure I would have been able to make every appointment. . .I think it might be a nice idea but I think you would find some scheduling challenges for people." [ID28]
Perceived benefit	". . .she actually did DIEP breast reconstruction, which is a huge surgery. By the next day she was able to lift her arms over her head, which for that population of patients, that takes months to do after surgery. So, she had said it was really because of the prehabilitation." [HCP2]
	"I really feel like I benefited a lot from it because it caught me in that time just after diagnosis when things were pretty scary and pretty awful and I felt like it was one of the key pieces of my plan for positivity during this whole thing, because it was setting a tone for recovery." [ID20]
Health behavior change	"I feel like being in programs like this [post-treatment rehabilitation], which started with the prehab, kept a momentum going. And, I'm not completely on my own yet, but it's great to have these kinds of programs at my disposal and it's helping me to stay active. I think prehab was the one to get that rolling." [ID16]
Regaining control	"I think for just the average person, it [prehabilitation] shares a lot of knowledge and I think knowledge is power and it gives someone the ability to take things into their own hands, where a lot of their control and power is being taken away from them." [ID01]
Prehabilitation as education	"You get some limited guidance from the surgeon and nurse about stretching and mobility exercises after the surgery, but it's not a lot. There was one group class and it's at a time when I probably wasn't that focused – the day before surgery – wasn't really focused on exercises. So, I thought it was helpful that I had the contact with you because it helped me figure out what I should do and that I should keep going." [ID28]

colleagues (25) found that 76% of their participants chose to exercise and of these, 85% exercised on three or more days per week. A recent review of prehabilitation prior to intra-abdominal cancer surgery reported that home-based trials had adherence rates of approximately 70% whereas supervised trials reported adherence rates of about 98% (49).

The participant satisfaction survey and qualitative findings from the interviews suggest that individuals had an extremely positive experience with prehabilitation. According to the satisfaction survey, all participants indicated that they (i) benefited from being in the study; (ii) felt like prehabilitation facilitated recovery after surgery; (iii) would recommend prehabilitation to anyone else with breast cancer who underwent surgery; and (iv) intended to continue exercising regularly (45–60 min per day, 3–4 days per week). These different perceptions of benefit also emerged in all of the participant interviews. Participants said that they felt like prehabilitation expedited their postoperative recovery and that they felt better during subsequent treatment(s) because of it. Although participants were not prescribed any postoperative exercise through the study, many indicated that they continued exercising during adjuvant therapy. For many participants in this study, participation in the prehabilitation program provided an opportunity to discuss safety concerns related to exercising during adjuvant treatment.

An important theme that was identified in the interviews was the need for a multimodal intervention, including exercise,

dietetic support, and stress management counseling delivered by the appropriate professionals. This need for multimodal prehabilitation has been repeatedly identified in the literature (50, 51). Advocacy from researchers and clinicians alike has resulted in a shift toward multimodal interventions in research and practice given that these different modalities likely were synergistically and provide greater benefit than either modality alone might (52, 53). In this study, participants highlighted the need for an exercise professional to be delivering information related to prehabilitation and rehabilitation, given that their oncology care providers may be unable to provide adequate information. A recent study by Nadler and colleagues (54) found that close to 80% of oncology care providers were unaware of cancer exercise guidelines for survivors and recognized a lack of knowledge, time, and concerns regarding safety as barriers to conversations surrounding exercise. As such, these health-care providers recognized the need for an exercise specialist to be included as part of the clinical team.

Prehabilitation as a catalyst for positive health behavior change also emerged as a prevalent theme expressed by participants in the qualitative investigation. Some participants reported that prehabilitation provided the momentum to make changes in health behaviors (e.g., exercise behaviors and diet habits) that they had been intending to make. Quantitative findings reflected these reports as seen by the changes in GLTEQ-LSI scores. These data suggest that there was an increase in self-reported physical activity between baseline and the preoperative assessment; at baseline, average GLTEQ-LSI scores for the study sample represented them as being insufficiently active [not meeting physical activity guidelines (55)].

While these are early findings which need confirmation via adequately powered randomized controlled trials, a few outcomes demonstrated clinically meaningful changes over the study period. Most notably, functional aerobic capacity scores increased well beyond clinically important margins from baseline to the preoperative assessment. There was a small decrease in 6MWT scores at the 6-week postsurgery assessment and subsequent increase in scores at the final study assessment. Importantly, scores did not return to baseline after surgery. Contemporary prehabilitation trials have largely included supervised exercise prescriptions. From those that have utilized home-based prescriptions similar to this study, increases in 6MWT scores in the preoperative period range from 25 to 42 meters over an average duration of around 30 days (53, 56, 57). While there are no normative values established for the 6MWT in this population, other trials of home-based exercise in the *posttreatment* setting have reported an average change of 60 m after a 12-week intervention with baseline values of approximately 417 m and post-intervention values of 477 m (58). The greater improvements in 6MWT scores in the present study may be explained by the high adherence rates compared to the aforementioned studies.

Self-reported disability was collected using the WHODAS 2.0 and DASH questionnaires which assess global and upper quadrant-specific disability, respectively. Scores from both measures reflected the greatest disability at the 6-week postoperative assessment. Changes in DASH scores from presurgery to postsurgery suggested a clinically important change in disability, which improved but did not return to baseline at the 12-week postoperative assessment. While there is substantial data supporting the use of physiotherapy after surgery to facilitate shoulder function recovery, (59–61) no studies to date have implemented this type of protocol preoperatively. Qualitative findings demonstrated that participants in this study continued to exercise after surgery, as reflected by the quantitative GLTEQ-LSI data. Presumably, this may have facilitated recovery of shoulder function as some participants stated in their interviews; however, it is difficult to ascertain this without a control group.

Health-related quality of life worsened slightly over the study period, as measured by the SF-36 questionnaire. These findings are in line with those from a review of surgical prehabilitation in a heterogeneous patient group which found that preoperative exercise interventions do not significantly affect HRQOL after surgery (62). Some data suggest that psychological prehabilitation might be beneficial in maintaining HRQOL before and after treatment (63). Taken together, these findings imply that a multimodal prehabilitation approach might be more helpful to address perioperative HRQOL and well-being, as suggested in the literature (50) and in the qualitative findings of the present study. Fatigue improved between baseline and the preoperative assessment but progressively worsened thereafter. The decline in scores at the 6-week postoperative assessment was the largest and reflected a clinically important change in fatigue levels. Treatment-related fatigue in cancer survivors is one of the most common and debilitating side effects of treatment, (9, 64) and in women with breast cancer, pretreatment fatigue is one of the strongest predictors of persistent fatigue after treatment (65). Exercise is established as one of the most effective interventions to mitigate cancer-related fatigue (66) but has yet to be used prophylactically. Data from the present study suggest that prehabilitation may improve fatigue levels prior to surgery; as such, it may have a role in attenuating persistent fatigue given the aforementioned relationship between pretreatment and posttreatment fatigue.

This study had several strengths including the novelty of the intervention in this population, the use of mixed methodology, which allowed for a comprehensive understanding intervention feasibility and participant experiences, and the inclusion of a large breadth of exploratory outcomes, which provide pilot data for sample-size calculations for future studies. Interpretation of findings, however, must be cautioned given the single-arm design which was underpowered to detect statistically significant changes in the included outcomes. The lack of between-group comparisons with an intervention-naïve group makes it impossible to comment on intervention efficacy, but the observed clinically meaningful changes warrant further investigation. In addition to the small sample size, there was a relatively high attrition rate in this study suggesting that the follow-up

timepoints may be difficult for participants to attend; this may be because individuals may be undergoing adjuvant therapy after surgery and experiencing radiation and chemotherapy-related adverse effects. Further, because participants were not reimbursed for study assessments, these visits may have been a financial burden that contributed to the high attrition rate. Other limitations include the late inclusion of qualitative interviews because of which we were unable to capture interview data from a large proportion of participants, especially those who had dropped/were not compliant; small qualitative sample which did not capture the breadth of the participants' experiences (i.e., those who participated in the interviews were those who were compliant and enjoyed the intervention); and self-reporting of exercise adherence and physical activity levels which, while common in exercise oncology literature, are often overreported (67).

CONCLUSION

Our data suggest that home-based prehabilitation prior to breast cancer surgery is feasible and favorably received by participants. For women undergoing breast cancer surgery, prehabilitation may facilitate postoperative recovery, impact health behavior change in the preoperative and postoperative periods, and improve physical activity levels and functional capacity both preoperatively and postoperatively. While these findings are encouraging and largely reflect previous prehabilitation research, adequately powered trials of multimodal prehabilitation in women with breast cancer are needed to confidently determine intervention efficacy.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because data collected cannot be shared outside of the research institution. Requests to access the datasets should be directed to corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University Health Network Research Ethics Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2020.571091/full#supplementary-material

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REVIEW
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Multiphasic Prehabilitation Across the Cancer Continuum: A Narrative Review and Conceptual Framework

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The field of cancer survivorship has significantly advanced person-centered care throughout the cancer continuum. Within cancer survivorship, the last decade has seen remarkable growth in the investigation of prehabilitation comprising pre-treatment interventions to prevent or attenuate the burden of oncologic therapies. While the majority of evidence remains in the surgical setting, prehabilitation is being adapted to target modifiable risk factors that predict poor treatment outcomes in patients receiving other systemic and localized anti-tumor treatments. Here, we propose a multiphasic approach for prehabilitation across the cancer continuum, as a conceptual framework, to encompass the variability in cancer treatment experiences while adopting the most inclusive definition of the cancer survivor.

Keywords: cancer, survivorship, prehabilitation, rehabilitation, oncology, continuum of care, conceptual framework, enhanced recovery after surgery

INTRODUCTION

For more than thirty years, cancer survivorship has grown to become a well-established and internationally endorsed component of gold-standard, person-centered care that starts at diagnosis and continues to end of life. The seminal report on survivorship by the Institute of Medicine and the National Research Council, entitled "From Cancer Patient to Survivor: Lost in Transition" recently celebrated a decade's worth of influence through its articulation of ten recommendations to improve oncology care (1). These recommendations specifically focus on the "period following first diagnosis

and treatment and prior to the development of a recurrence of the initial cancer or death", in response to insufficient attention to patients' needs during this time. With remarkable progress in this field, pause for reflection on the application of survivorship principles at the core of these recommendations (*e.g.*, strategies to "identify and manage late effects of cancer and its treatment") (2) is warranted, particularly, how these principles apply to the periods *between* diagnosis (*i.e.*, primary, recurrence, and second primary) and treatment(s).

Cancer rehabilitation programs aim to help a person maximize physical, social, psychological, and vocational functioning within the limits imposed by cancer and its treatment (3) and are often the crux of cancer survivorship services. Because the field of cancer rehabilitation predates survivorship terminology, its integration (although still a work in progress) reflects its medical origins in impairment-driven care. While representing a marked advancement in oncology, contemporary cancer rehabilitation has largely been reactive to treatment sequelae rather than proactive in preventing or attenuating anticipated consequences of common treatments. The 'future' of cancer rehabilitation in 1974 highlighted approaches to prevent or minimize disability that could be reasonably predicted; however, only recently have 'rehabilitation' models been proposed in which services are initiated at the time of diagnosis and continued throughout the continuum of treatment (4, 5). The focus of recent interventions on building resilience *prior to* treatment through conditioning and medical optimization is commonly referred to as *pre*habilitation.

Cancer prehabilitation is defined as "a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment, includes physical and psychological assessments that establish a baseline functional level, identifies impairments, and provides targeted interventions that improve a person's health to prevent or reduce the incidence and the severity of current and future impairments" (6). Prehabilitation is not oncology-specific, but is a growing field unto itself that has historically been applied to surgery, where preoperative physiological and psychosocial health are well-established predictors of peri- and postoperative outcomes (7, 8). Systematic reviews of prehabilitation in surgical oncology provide encouraging findings such as improved functional capacity, maintenance of lean mass, length of hospital stay, surgical complication rates, and health-related quality of life (HRQoL); however, methodological limitations have led to cautious interpretation (9–13).

The rapid growth of cancer prehabilitation research over the past decade has contributed to a push for clinical implementation within perioperative care models (14, 15) despite gaps in foundational prehabilitation frameworks that may limit its impact in practice. First, while prehabilitation models have nearly exclusively focused on the period between diagnosis and surgery, cancer is often treated with multiple lines of therapy, each with unique treatment-related sequelae and challenges to completion. Accordingly, multiple phases of prehabilitation may be needed to prepare for consecutive treatments and their unique anticipated adverse effects. Whereas referral or invitation to prehabilitation may currently reside with perioperative care physicians (*e.g.*, anesthetists and surgeons), extending prehabilitation to neoadjuvant and adjuvant treatments may offer opportunities for other physicians (*e.g.*, medical or radiation oncologists) to direct their patients to prehabilitation. Second, while prehabilitation may become an integral part of survivorship care, it does not intend to replace post-treatment rehabilitation, but rather, aims to complement it (**Figure 1**). For example, prehabilitation may include the education on early ambulation after surgery or the introduction of rehabilitation exercises so that patients are familiar with what to expect and how to perform these activities early in their postoperative recovery. Similarly, rehabilitation may capitalize on behavior change strategies introduced prior to treatment for long-term maintenance of

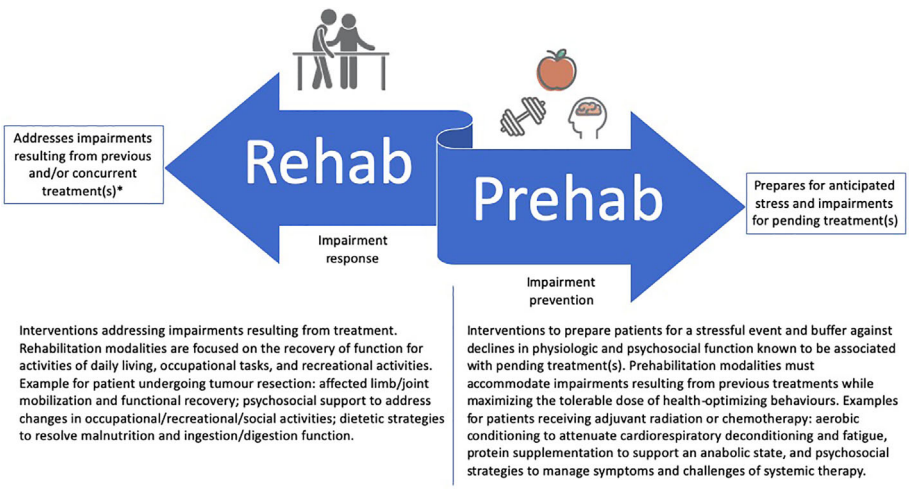


FIGURE 1 | Example of coordinated rehabilitation and prehabilitation between two treatments.

health behaviors. It is therefore imperative that the two care approaches (rehabilitation and prehabilitation) work in a coordinated fashion before and after treatment to maximize their synergy and respective benefits for patients.

Prehabilitation has also rarely included the breadth of the 'cancer survivor' definition, focusing exclusively on the patient, and is not yet inclusive of their caregivers (*i.e.*, family and friends) (16). Many related caregivers of people with cancer experience burnout and caregiver fatigue (17), with levels of psychological distress equal to or often even greater than those seen in the patient (18). The caregiver can experience stress related to disease and treatment cycles that accumulates over time towards an increased risk for illness and psychological morbidity (19), owing to medical (*e.g.*, the unknown regarding diagnosis, prognosis, and clinical course), practical (*e.g.*, financial planning), psychosocial (*e.g.*, resolving family conflict) and spiritual/religious uncertainty (20, 21). Unfortunately, supportive care interventions for those affected but not diagnosed with cancer are lacking despite a reduced ability to partake in self-care behaviors (22, 23). A meta-analysis of randomized trials, found that caregivers who receive interventions (including psychoeducation, skills training, and therapeutic counseling) either independently or in conjunction with the patient, experience reduced caregiver burden, distress and anxiety, and improved coping and physical functioning (24, 25). It may be argued that prehabilitation's benefit for the patient could likely be further enhanced through extension of similar services to caregivers who may be able to support prehabilitation for the patient as well as become more capable of attending to the peri- and post-treatment needs of the patient.

To support evolving clinical and research endeavours in prehabilitation for cancer survivors, we propose a complement to current conceptual frameworks and definitions of prehabilitation (26, 27). The novel contributions of this framework highlight the dynamic and multiphasic potential for prehabilitation that can be applied broadly to the cancer survivor, inclusive of the patient, family, friends and caregivers (16). For the purposes of this paper, we refer to persons receiving cancer treatment(s) as the patient to distinguish them from other cancer survivors. In the sections that follow, we briefly review prehabilitation as a personalized, multimodal intervention, as well as provide an overview of the evidence and theoretical rationale for multiphasic prehabilitation planning, organized by phase of treatment (*i.e.*, neoadjuvant, primary, and adjuvant treatment).

MULTIMODAL PREHABILITATION

While early prehabilitation trials were predominantly unimodal (*e.g.*, exercise or diet alone), contemporary prehabilitation models have adopted a multimodal approach to address the complex needs of people with cancer. Multimodal prehabilitation may be defined as the incorporation of two or more intervention components specifically selected for their potential cumulative or synergistic effects on health outcomes. Multimodal prehabilitation interventions have often comprised a combination of the following: i) aerobic and resistance training to attenuate cardiorespiratory and musculoskeletal deconditioning, respectively; ii) dietary interventions to counteract disease and/or treatment-related malnutrition and to support anabolism and the metabolic cost of exercise; iii) psychological interventions to reduce stress and associated morbidity; iv) cessation of adverse health behaviors (*e.g.*, alcohol abuse, smoking); v) medical optimization (*e.g.*, assessing/treating anemia; medication corrections); and vi) behavioral counseling to support intervention initiation and adherence in the pre-treatment setting and establish self-management skills for long-term health behavior maintenance (28–30). While these recommendations are largely driven by expert consensus, recent qualitative findings from patient interviews also support the need for an integrated multimodal approach to prehabilitation (31). These findings are congruent with previous research which suggests that comprehensive prehabilitation support *via* complementary modalities was especially important and well received by people undergoing surgery for lung and colorectal cancer (32).

Inherently, the delivery of multimodal prehabilitation in cancer is expected to incorporate multiple health practitioners that include the oncology physicians (*e.g.*, surgeons, medical oncologists, radiation oncologists, and haematology oncologists) and other medical specialists (*e.g.*, anesthesiologists, geriatricians, physiatrists, and psychiatrists). In addition to physicians, health professionals that direct or deliver specific prehabilitation modalities are also essential. Professions and their respective roles in prehabilitation may include physiotherapists, occupational therapists, kinesiologists, exercise physiologists, dietitians, nutritionists, psychologists, social workers, pharmacists and nurses. To address the needs of the non-patient cancer survivors (*i.e.*, friends and family), health professionals outside of the tertiary care setting may be best suited to prehabilitate for physical or psychological conditioning to support caregiving, bereavement preparation, and/or estate management. Finally, at the heart of person-centered care is engagement of the person with cancer, which represents an essential element of appropriately co-designed interventions and shared decision making. Co-design of prehabilitation interventions by healthcare practitioners and cancer survivors is recommended to cultivate a sense of purpose and responsibility towards managing one's health *with*, rather than *by*, the healthcare team. Incorporating the patient and caregivers into care planning is aligned with the WHO interprofessional practice definition and supports engagement of cancer survivors towards self-managed behaviors (33).

PREHABILITATION PRIOR TO SURGERY AND OTHER PRIMARY TREATMENTS

Despite the breadth of anti-tumor approaches and their distinct consequences to the patient, research on multimodal prehabilitation has almost exclusively focused on surgery. The

pre-surgical focus may be explained by the opportunity that wait-times afford to invest in prehabilitation for improvements in peri- and post-treatment health, and potential economic advantages of reduced surgical complications, postoperative morbidity, and length of stay. Addressing modifiable surgical risk factors (such as exercise intolerance, malnutrition, anemia, smoking, and medication usage) have demonstrated a profound effect not only on postoperative HRQoL, but also morbidity, mortality, and the need for further care (34–36). Consequently, surgical prehabilitation has often been thoughtfully tailored to target specific risk factors. For example, surgical prehabilitation commonly includes training to improve cardiorespiratory fitness to prepare the patient for the impending surgical stress response characterized by increased cardiac output and oxygen consumption (37, 38) and because of its established relationship with post-operative morbidity, mortality, and hospital length of stay (39, 40). As a result, cardiorespiratory fitness is often used as a physiological indicator of intervention efficacy.

Systematic reviews of surgical prehabilitation, including both unimodal and multimodal approaches for people with cancer, conclude that prehabilitation improves physical fitness and functional capacity, with lesser, yet still compelling, data to suggest potential improvements in hospital length of stay, post-surgical complication rates, post-operative recovery and HRQoL when compared to usual care or post-operative rehabilitation alone (9–12). The evidence is challenged by limitations in methodological quality, namely small sample sizes, heterogenous interventions and endpoints, and narrow inclusion criteria that limit generalizability. Consequently, prehabilitation has garnered only a weak recommendation for integration into contemporary perioperative care pathways (*e.g.*, Enhanced Recovery After Surgery; ERAS) (41). Moreover, given that many studies fail to appropriately describe safety or adverse events, and higher-risk participants have often been excluded, the actual risk or benefit of prehabilitating frail patients who may need it most is still uncertain. Advancement towards clinical adoption will benefit from ongoing international efforts *via* phase III clinical trials (42–44), as well as improved reporting of safety outcomes, inclusion of higher-risk study populations, well described implementation strategies, and comparisons of multimodal to unimodal strategies that attempt to delineate modality-specific benefit.

Beyond surgery, prehabilitation prior to stem cell transplant (SCT) has received growing research attention given that SCT is a cornerstone haematological cancer management that often follows high-dose chemotherapy or whole-body radiation. The 'dual hit' of treatment leaves patients severely deconditioned, where impairment is more apparent in those with poor physical function prior to transplant (45). While interventions delivered after SCT attempt to remediate deconditioning and dysfunction are more widely studied, researchers have also examined prehabilitation exclusively prior to SCT (46–48) or in combination with post-transplant interventions (49–51). Such studies have featured a combination of supervised and self-administered multimodal interventions, comprised of low-to-moderate intensity endurance and resistance training, stress management and relaxation, as well as dietary guidance. The available evidence suggests that prehabilitation for SCT is feasible and may offer favourable changes in physical fitness, psychosocial distress, fatigue, HRQoL and hospital length of stay; however, more research is needed to verify early findings (50). It is worth highlighting that, despite feasibility successes, the research acknowledges significant challenges in delivering prehabilitation prior to SCT in light of the often markedly poor and often changing health status of SCT candidates.

While the surgical and SCT settings currently form the evidence-base for multimodal prehabilitation for primary therapy, comparable preparatory interventions for primary radiation or chemotherapy (among others) remain largely unexplored. It is worth highlighting that the iatrogenic consequences of radiation and chemotherapy may have a more gradual onset than the more abrupt insult of surgery and SCT, and thus the metrics of success may be different across treatments. For example, outcomes of interest in non-surgical contexts, such as chemotherapy or radiotherapy, may prioritize other markers of efficacy, such as dose tolerance, discontinuation of treatment course, and patient-reported health over several weeks of active treatment (*e.g.*, fatigue, cardiovascular function, and psychological health).

PREHABILITATION DURING OR AFTER NEOADJUVANT THERAPY

Neoadjuvant treatment (NAT; commonly comprising chemo- and/or radio-therapy after surgery, for example) toxicities manifest, in part, as reduced cardiorespiratory and musculoskeletal fitness stemming from underlying tissue, organ, and cellular dysfunction (52–54). Early evidence indicates that this cardiorespiratory deconditioning is associated with an increased risk of surgical complications and peri- and post-operative morbidity and mortality (53, 54). Importantly, cardiorespiratory fitness does not naturally recover between the end of NAT and the time of surgery (55), but rather, continues to decline in the absence of intervention (56). In addition to impaired cardiorespiratory fitness, compromised nutritional status resulting from NAT is common and can worsen physiological dysfunction (57) and affect surgical eligibility (58). Ultimately, NAT creates a more frail, nutritionally compromised surgical candidate that is more likely to have a worse surgical experience. The benefits of prehabilitation in this setting may include the mitigation of NAT-induced deconditioning and consequently promote an earlier and fuller recovery prior to surgery. One practical consideration for prehabilitation in this context is that NAT is often initiated shortly after diagnosis when it may be impractical to routinely intervene prior to its initiation. While initiating prehabilitation prior to NAT may be ideal, there is a growing body of evidence highlighting the health benefits of exercise, enhanced nutrition, and psychology during and after radiation and chemotherapy (59, 60). Collectively, the data suggest that

starting prehabilitation during this period with targeted outcomes for both neoadjuvant and primary treatments is likely beneficial.

Interventions aimed at mitigating or preventing associated physiological and psychosocial deconditioning related to NAT have not consistently been described as 'prehabilitation', making it difficult to synthesize the relevant literature (61). To our knowledge, exercise delivered concurrently with NAT has been examined in five studies with small samples sizes and variable methodological quality (62–66). Early findings suggest that supervised exercise prehabilitation during NAT is safe, feasible, and may maintain or improve cardiorespiratory fitness over the intervention period. Recently, West and colleagues (56) examined the role of prehabilitation exclusively in the post-NAT/pre-surgical setting in 22 people with rectal cancer who participated in six weeks of facility-based, high-intensity interval training and were compared to 17 usual care participants in a non-randomized trial. Those who participated in prehabilitation recovered cardiorespiratory fitness to baseline levels prior to surgery, whereas usual care participants exhibited suppressed aerobic capacity. These early data highlight the amenability of prehabilitation during this stage of the cancer continuum, given that NAT may be delivered over several months, with a relatively quick and dramatic deconditioning effect, making patients progressively more vulnerable to poor surgical outcomes (52–54). In light of the encouraging early findings, prehabilitation during or after NAT appears to be the most rapidly developing area of the field.

PREHABILITATION PRIOR TO ADJUVANT TREATMENT

Commencement of early rehabilitation following primary therapy with synchronous or sequential prehabilitation for adjuvant therapy is likely to have both distinct yet complementary functions as shown in **Figure 2**. The initiation of adjuvant therapy is commonly contingent upon recovery and functional status following primary therapy (67, 68), which is important because delayed adjuvant therapy can affect survival (69). It is essential to highlight that re- and prehabilitation in-between primary and adjuvant therapy, are neither mutually exclusive nor synonymous because of their distinctive health objectives. For example, rehabilitation following resective surgery may be required to restore localized mobility and strength, whereas prehabilitation for adjuvant chemotherapy may focus on optimizing cardiorespiratory function to protect against chemotherapy-induced cardiotoxicity. Given that cardiotoxicity can adversely affect tumor control due to reduced dosage amidst concerns of deteriorating cardiac function (70), improving preoperative cardiac resilience appears to be an important strategy as demonstrated in a small, but growing body of pre-clinical research (71–75). Proof-of-concept in humans has recently been demonstrated in a small randomized controlled trial in women with breast cancer, which found that a single bout of vigorous-intensity exercise acutely prior to anthracycline administration attenuated cardiac damage (76). To our knowledge, no studies have specifically examined prehabilitation prior to adjuvant therapy.

Prehabilitation for adjuvant treatment may be particularly beneficial given the compounded deconditioning associated with multiple lines of therapy; and, as a result, these interventions might provide the opportunity to mitigate the catabolic losses and associated consequences of anti-cancer treatments. Martin et al. (77) found that in a cohort of 1,473 people with lung and gastrointestinal cancer exhibiting weight loss, low muscle mass, and low muscle density, survival was just 8.4 months, compared with 28.4 months in patients who had none of these characteristics. Similarly, Prado and colleagues (78) demonstrated that, in patients with metastatic breast cancer receiving capecitabine, the prevalence of dose-limiting chemotherapy-related toxicity in sarcopenic patients was more than twice that of non-sarcopenic patients. Evidence in this setting is limited, but preclinical studies suggest biological plausibility of benefit against chemotherapy-induced cardiotoxicity (71–73); however, human clinical trials are needed for confirmation. In the psychological domain, the deleterious effects of chemotherapy and radiation therapy are well described. In the pre-adjuvant treatment setting, recent findings suggest that approximately one half and one third of patients have anxiety or depression, respectively (79). Importantly, these findings noted the predictive value of demographic factors that warrant

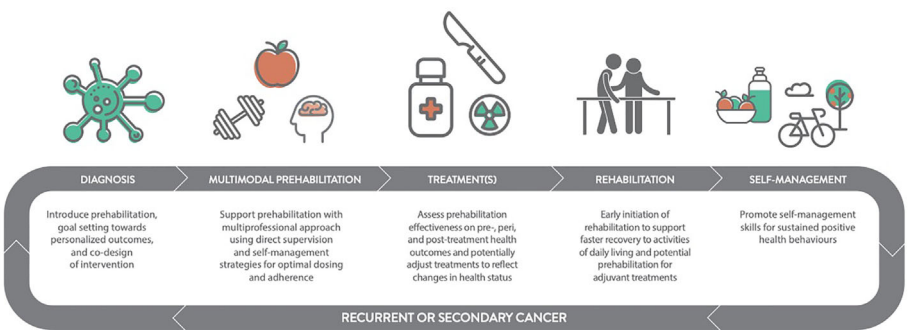
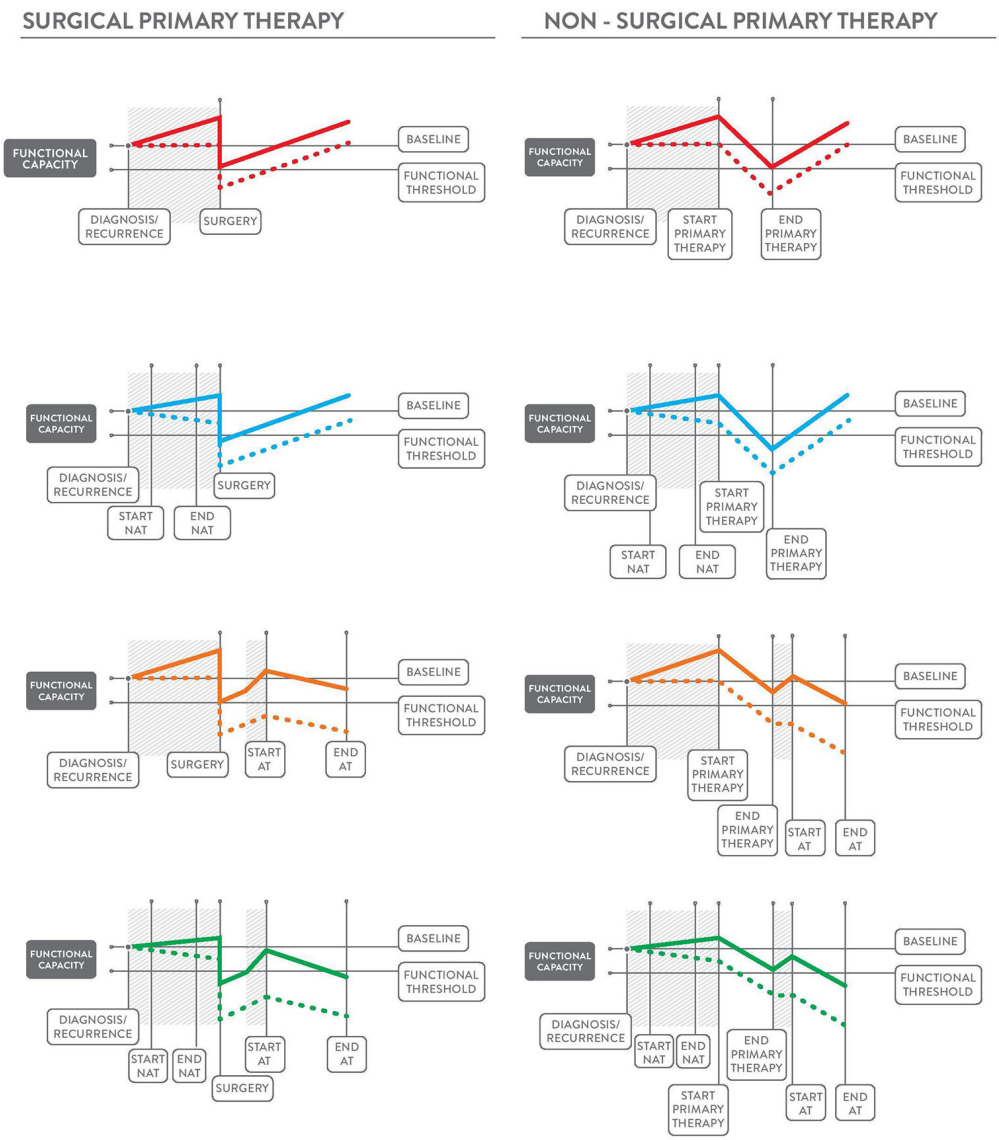


FIGURE 2 | Prehabilitation within the Cancer Continuum (Including Recurrence or New Primary Cancers).

consideration for the appropriate tailoring of interventions targeting mental health prior to adjuvant treatment. Studies have also shown that anxiety can be precipitated by concerns regarding physical function and maintaining social roles (80) as well as the financial toxicity of treatment (81), which may be prolonged in long-course adjuvant treatment and could be targets for prehabilitation. There has been little research on psychological prehabilitation prior to adjuvant treatment; however, a recent systematic review and meta-analysis of randomized controlled trials found that "prophylactic" pharmacotherapy, psychotherapy, and other interventions, including exercise, prevented or mitigated depression for those undergoing cancer treatment (82).

MULTIPHASIC PREHABILITATION: A CONCEPTUAL FRAMEWORK

Multiphasic prehabilitation, as a novel and complementary conceptual framework for the field, is depicted in the panels of **Figure 3**. It incorporates and extends early and revised models of



The figure depicts the theoretical opportunity of multimodal-multiprofessional prehabilitation (solid lines), compared to no prehab (dashed lines) to improve functional capacity for a given treatment experience. 'Functional capacity' refers to any measure that could be vulnerable to treatment insult and sensitive to prehabilitation intervention. A prehabilitation window is represented by the shaded areas. Surgical and non-surgical primary therapies are represented in the left and right panels, respectively. AT = adjuvant therapy; NAT = neo-adjuvant therapy

FIGURE 3 | Prehabilitation Across the Cancer Continuum.

prehabilitation described by Carli and colleagues (26, 27) and the cancer-specific definition by Silver, Baima, and Mayer (83) to provide an evidence and theory-informed application of prehabilitation across the entire cancer continuum. This framework is intended to guide future research by connecting the burgeoning data that show the benefit of healthier cancer survivors prior to different treatments and combinations of treatments with the body of evidence on modifiable risk factors for adverse treatment- and health-related outcomes. Core to the multiphasic concept is that prehabilitation may be considered as a health optimizing strategy that can occur multiple times following an initial cancer diagnosis. Multiphasic prehabilitation is an innovation to initial conceptualizations that has yet to be empirically tested as a cohesive sequence of preparatory measures across treatment exposures. Nevertheless, it is intended to provoke investigation of proactive interventions that focus on periods of relative health where the 'maximum tolerable dose' for a health intervention can be pursued more readily in the absence of active treatments that often erode functional capacity, appetite, mental health and motivation. Multiphasic prehabilitation requires nuance and tailoring to the existing and anticipated experiences at each phase of the cancer journey to minimize treatment-related side effects and subsequent treatment delays, thereby improving wellbeing and potentially prognosis over the long term. Aggressively preparing for repeated challenges across the trajectory of survivorship with multiphasic prehabilitation may be akin to periodization training models of high-performance sport with cyclic rounds of training prior to competition, both with similar goals: to optimize health preceding an anticipated stressor to ensure 'maximal performance' and rapid recovery.

FUTURE DIRECTIONS IN PREHABILITATION RESEARCH

The efficacy for prehabilitation on health and economic outcomes has been best demonstrated in the surgical setting; however, limitations in methodological quality must be addressed to compel widespread adoption into perioperative care. Emerging areas of prehabilitation in oncology, including prehabilitation prior to non-surgical anti-tumor treatments have shown promising findings and justify further examination, including within the context of a multiphasic approach. As the volume and quality of evidence describing the benefits of prehabilitation mounts, important information about its delivery in a clinical setting is needed. Methodologies that assess complex interventions, such as process evaluations as highlighted by the Medical Research Council (84) will permit greater understanding of biological, psychological, social and behavioral ('biopsychosociobehavioral') factors that drive prehabilitation participation, adherence, and medical outcomes in complex healthcare settings. Similarly, implementation science methodologies, as well as research within the context of clinically integrated programs, will add rich evidence to the understanding of how prehabilitation can be incorporated into standard of care as well as impacts on patient and economic outcomes. Examples of prehabilitation programming are occurring worldwide, including initiatives in Australia (85), Canada (32), Denmark (86), Japan (87), the Netherlands (88), Spain (89), the United Kingdom (90), and the United States (91, 92). Finally, across all research designs and settings, important gaps in research include: i) a better understanding of the differences between unimodal and multimodal prehabilitation and for which cancer survivors these should be applied; ii) strategies to identify and adapt prehabilitation for 'non-responders'; iii) prehabilitation for non-patient cancer survivors whom are likely to experience significant decline in aspects of their health when supporting a patient; and iv) the mechanisms of benefit of prehabilitation for cancer survivors.

CONCLUSION

The concept of prehabilitation has rapidly ascended into the common lexicon of survivorship care with research across cancer types, treatments, and modalities. The proposed conceptual framework for prehabilitation aims to guide further investigation of the viability and impact of repeated, pre-treatment interventions that target improved health outcomes throughout the entire cancer continuum.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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The Role of Behavioral Science in Personalized Multimodal Prehabilitation in Cancer

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Multimodal prehabilitation is increasingly recognized as an important component of the pre-operative pathway in oncology. It aims to optimize physical and psychological health through delivery of a series of tailored interventions including exercise, nutrition, and psychological support. At the core of this prescription is a need for considerable health behavior change, to ensure that patients are engaged with and adhere to these interventions and experience the associated benefits. To date the prehabilitation literature has focused on testing the efficacy of devised exercise and nutritional interventions with a primary focus on physiological and mechanistic outcomes with little consideration for the role of behavioral science, supporting individual behavior change or optimizing patient engagement. Changing health behavior is complex and to maximize success, prehabilitation programs should draw on latest insights from the field of behavioral science. Behavioral science offers extensive knowledge on theories and models of health behavior change to further advance intervention effectiveness. Similarly, interventions developed with a person-centered approach, taking into consideration individual needs and preferences will increase engagement. In this article, we will provide an overview of the extent to which the existing prehabilitation literature incorporates behavioral science, as well as studies that have explored patient's attitudes toward prehabilitation. We will go on to describe and critique ongoing trials in a variety of contexts within oncology prehabilitation and discuss how current scientific knowledge may be enhanced from a behavioral science perspective. We will also consider the role of "surgery schools" and detail practical recommendations that can be embedded in existing or emerging clinical settings.

Keywords: prehabilitaion, behavior change, behavioral science, co-design, interventions, oncology, cancer

INTRODUCTION

Despite advancements in cancer therapies and surgical techniques 15–40% of cancer patients who undergo surgical treatment experience postoperative complications (Hughes et al., 2019). This can lead to increased hospital stay, hospital readmissions and detrimental effects on quality of life, physical functioning and psychosocial outcomes (Durrand et al., 2019). Multimodal prehabilitation is increasingly recognized as an important component of the pre-operative pathway in oncology. It aims to optimize physical and psychological health through delivery of a series of tailored interventions including exercise, nutrition, and psychological support.

Historically evaluations of the efficacy of prehabilitation have focused on physiological outcomes and physiological mechanisms of action. However, multimodal prehabilitation programs require significant patient engagement. Firstly, patients must choose whether to participate and then engage with multifactorial behavior change in order to adhere, for example, to exercise regimes and dietary changes.

Changing health behaviors is complex and requires much more than provision of information. Interventions that seek to support individual behavior change are most effective when they draw on behavioral science (National Institute of Clinical Excellence (NICE), 2014). Furthermore, interventions developed with a person-centered approach, considering individual needs and preferences will increase patient engagement and are more effective than expert only design processes (Trischler et al., 2018).

This paper describes the existing evidence on patient experience and attitudes toward prehabilitation. We illustrate how inclusion of behavioral science could strengthen uptake and adherence to prehabilitation programs, as well as current evidence of integration of this discipline in the field, both in research and clinical settings.

MODES OF PREHABILITATION DELIVERY AND PATIENT EXPERIENCE

The optimal mode for providing interventions to enhance physical and psychosocial wellbeing of people with cancer continues to be debated.

Supervised in-person programs delivered via health professionals are arguably considered the gold standard in terms of safety and efficacy (Cormie et al., 2018; Newton et al., 2018). Furthermore, there is evidence that those who are willing and able to participate in such programs experience significant benefits beyond physiological optimization, such as improvements in quality of life, cultivating a positive attitude and fostering a strong sense of purpose (Burke et al., 2013). However, delivery costs are prohibitive, and few programs are available (Dennett et al., 2017). There is also consistent evidence that cancer patients face barriers to attending in-person supervised programs. These include transportation, parking and time, as well as a desire to avoid additional hospital appointments (Ferreira et al., 2018). Some cancer patients express a preference for flexible home-based programs (Hardcastle and Cohen, 2017) however a study exploring the experiences of such a program recounts some patients felt a greater involvement from health care professionals would increase engagement, particularly if they were lacking "energy" or "willpower" (Beck et al., 2020). The fundamental issue spurring the debate is that no one delivery mode offers a program that is effective, safe, person-centered, and widely accessible.

Given the inherent challenges with all approaches, we argue that debating the optimal delivery mode is a moot, counterproductive activity. Rather, attention should be paid to how the limitations of any delivery mode can be addressed, so that programs that best suit the local context can be provided. Many prehabilitation trials described below addressed this by offering a hybrid program, combining supervised sessions and home-based elements. Community based programs that offer more locally available support have also shown positive preliminary results (Loughney et al., 2019). Furthermore, the use of technology is increasing and will likely help to address benefit gaps with distance/home-based programs. In the field of cardiac rehabilitation for example, an approach utilizing sensors and a mobile application to provide real-time supervision of aerobic activity in the local environment was non-inferior to a standard in-clinic approach, was cheaper to deliver and resulted in longer-term behavior change (Maddison et al., 2019).

As a result of the Covid-19 pandemic we will likely see rapid advances in remote delivery of cancer-specific interventions. Prehabilitation clinical teams have responded with agility and adapted programs to online delivery modes. For example, the St Georges Get Set 4 Surgery program (St George's University Hospital NHS Foundation Trust, 2020) used a battery of short videos to continue providing information and advice to their patients. The Perioperative Team at University Hospital Southampton NHS Foundation trust were forced to pause a large prehabilitation randomized controlled trial (Wessex Fit-4-Cancer Surgery trial) (ClinicalTrials.gov, 2018) and developed the SafeFit Trial, which consists of a multi-modal intervention delivered virtually by video conferencing and telephone support (ClinicalTrials.gov, 2020). These changes in service delivery present unique opportunities to add to the evidence-base regarding remote delivery of cancer-specific prehabilitation.

Ultimately, delivery mode decisions will depend on local context and should be based on a needs analysis and consultation with all relevant stakeholders, including the end users. This is exemplified by Tang et al., in their co-design of a prehabilitation service for prostate cancer patients (Tang et al., 2020) and the Manchester Prehab4Cancer clinical service (Moore et al., 2020).

THE ROLE OF THEORIES AND FRAMEWORKS OF BEHAVIOR CHANGE

Once the mode of program delivery has been determined attention can move to identifying the "active ingredients" or individual program components required to meet its objectives. Program developers will have a number of key questions such as:

- How can we encourage uptake to prehabilitation? Especially among patients who stand to benefit the most.
- What are the implications for trying to change multiple health behaviors at once? Should behaviors be changed sequentially (if time allows) or simultaneously?
- How can we promote longer-term behavior changes that will assist with recovery after the operation and reduce the risk of further health issues?

Behavioral scientists are trained in behavioral analysis and the application of intervention planning frameworks like intervention mapping (Bartholomew et al., 1998) which can facilitate this process of intervention development. Like interventions developed within medicine, at the core of such frameworks are: (1) the identification of determinants of the outcome and (2) the identification and application of strategies that effectively target these determinants. Theories of behavior change can help identify appropriate determinants of behavior and strategies to influence those behaviors.

These strategies or "active ingredients" are often referred to as behavior change techniques (BCTs) defined as "an observable, replicable, and irreducible component of an intervention designed to alter or redirect causal processes that regulate behavior" p23 (Michie et al., 2013). Examples include goal setting, graded tasks (set easy to perform goals that get increasingly difficult until the behavior is achieved) and self-monitoring (a method to monitor and record behavior). Michie et al. (2013) developed a Taxonomy of Behavior Change Techniques providing a common language to describe approaches to support behavior change and facilitate synthesis of evidence to support the design of future interventions. Theories and frameworks of behavior change and empirical evidence can guide identification of the most effective BCTs to address the relevant processes that regulate behavior (determinants), which will vary depending on the ambitions of the program and the characteristics of participants.

A discussion of relevant theories and research evidence for addressing prehabilitation objectives is beyond the scope of this article. Rather, it is our intention to highlight that these questions are the remit of behavioral scientists, and to showcase what integration of this expertise into practice might look like. As with all multidisciplinary teams, there can be tensions between disciplines. For example, the clinical team may be focused on the optimal intervention or stimulus for increasing cardiorespiratory fitness prior to surgery, whereas the behavioral expert may prioritize the optimal intervention to maximize motivation. Furthermore, if an ambition of the program is to promote longer-term behavior change patients need to develop skills to engage in these behaviors autonomously. This may be at odds to a highly supervised and structured approach that may be favored by others in the team. By working together, an appropriate balance can be achieved and ultimately enhance program effectiveness.

Relevant input from a behavioral scientist in this context may include integration of strategies for enhancing autonomy, competence, and control within the prescribed program. This could include for example, allowing choices where possible, setting graded tasks, and in the context of exercise, prescribing affect-regulated exercise [i.e., an intensity that feels good (Parfitt et al., 2012)]. These strategies should enhance enjoyment of the program and in doing so increase the likelihood of on-going behavior change (Teixeira et al., 2012). Incorporating strategies to promote habit formation could also help to achieve longer-term outcomes (Gardner et al., 2012). Furthermore, a psychological determinant of behavior change that has received considerable attention is self-efficacy. Defined as " the belief in one's capabilities to organize and execute the courses of action required to produce given attainments," self-efficacy has been established as one of the most consistent predictors of adoption and maintenance of physical activity behavior (van Stralen et al., 2009). Studies exploring patient perceptions and experience of prehabilitation programs describe high motivation to engage but confidence to do so as low, hindering engagement (McDonald et al., 2019; Beck et al., 2020). As such, methods to increase self-efficacy to engage in the behaviors required of prehabilitation programs is likely to improve uptake and action. With training, exercise professionals delivering the interventions can incorporate these approaches throughout the program thus maintaining fidelity of the exercise "dose" whilst increasing patient empowerment.

In addition to empirical evidence and theories of behavior change to guide intervention development it is crucial that patients are consulted, thus maximizing engagement and implementation. Several frameworks are available to support such co-creation, including the Person-Based Approach (Yardley et al., 2015). Developed by international leaders in the field of behavioral science, central to the Person-Based Approach is ensuring the needs of the end users are understood and incorporated. This is achieved by using iterative qualitative research (such as interviews and focus groups) at every stage of intervention development and implementation, allowing identification of the key barriers and facilitators to engagement and BCTs to address these (Yardley et al., 2015). Adopting such an approach will help ensure the final program is salient, persuasive, relevant, and achievable for patients.

Working alongside clinical colleagues, a behavioral scientist is well-placed to employ intervention mapping processes, behavioral analysis and patient-centered intervention development. They can also provide training to colleagues delivering the programs to ensure the identified BCTs embedded within it are employed appropriately. This is vital to the integrity of the intervention. For example, when using the BCT of goal setting the process must be collaborative and supportive, enabling the patient to identify salient goals that are meaningful to them. If the goals are directed by the health care professional without appropriate active listening to the patient's needs and circumstance the process is unlikely to be effective. See **Figure 1** which illustrates the key principles of behavioral science that can be embedded in the planning, optimisation and evaluation of prehabilitation programs.

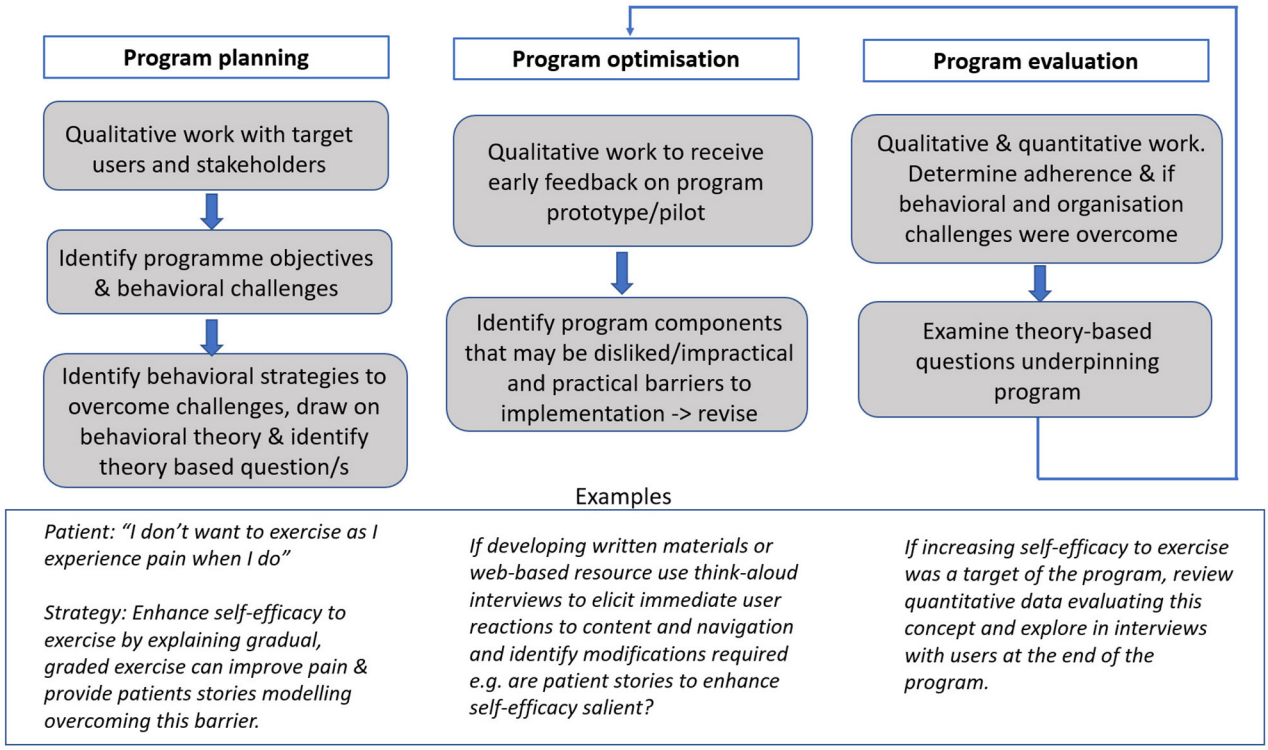

FIGURE 1 | Embedding behavioral science in program planning, optimization, and evaluation.

RECENT AND ONGOING PREHABILITATION TRIALS

In 2018, a comprehensive review of prehabilitation trials was undertaken to inform the development of the Principles and Guidance for Prehabilitation (Macmillan Cancer Support., 2019). As described by Copeland et al. (2020) interrogation of this literature revealed a paucity of consideration of behavioral science. No studies explicitly describe components of the intervention as per the BCT taxonomy. However, in a minority of studies strategies to enhance intervention compliance were included, for example using self-monitoring strategies. However, any behavior change support was poorly described, and none specified the underlying behavioral determinants being targeted.

Examining the literature published since 2018 paints an evolving picture (see **Table 1**). While many recent and ongoing trials do not include reference to behavior change support there are notable exceptions. Barberan-Garcia et al. (2020) describe a personalized program to promote physical activity in moderate-to-high risk lung cancer patients undergoing thoracic surgery. They report inclusion of behavior change strategies including self-monitoring; comparison of behavior with goal; a daily motivational message; positive reinforcement once a goal is achieved; and provision of educational material. In addition, the cognitive behavioral therapy included in the program aims to "reinforce patients' motivation... and to foster patients' engagement for healthy lifestyles" p. 4 (Barberan-Garcia et al., 2020). Furthermore, in an ongoing trial described by McCourt et al. (2020) the role of behavioral science is explicitly described. This study will investigate the feasibility of exercise-based prehabilitation prior to stem-cell transplantations in myeloma patients. Strategies to promote adherence to the intervention and to change exercise behavior are described as per the BCT taxonomy. Similarly, Macleod et al. (2018) report results of a feasibility trial among adults with stage I–III colorectal cancer. The TreatWELL intervention targeted smoking, alcohol, physical activity, diet, and weight management. The authors describe behavioral approaches informed by self-regulatory theory and the health action process approach. Additionally, the behavior change wheel (a synthesis of 19 behavior change frameworks) (Michie et al., 2011) was used to identify BCTs to motivate and support lifestyle change.

Importantly, some of the aforementioned studies also include qualitative process evaluations (Macleod et al., 2018; Brahmbhatt et al., 2020; McCourt et al., 2020). Brahmbhatt et al. (2020) present findings from interviews with participants who had participated in a home-based exercise prehabilitation program prior to breast cancer surgery. They appreciated the personalized exercise prescription which they could complete with ease, irrespective of pervious activity levels. In-person instruction on how to perform the exercise increased participant's confidence to exercise independently at home. Motivation, lack of time, and the weather were identified as barriers to participation. McCourt et al. (2020) plan to interview patients to explore experiences

TABLE 1 | Recent[a] and ongoing prehabilitation studies in cancer care: role of behavioral science.

Authors, (Year) protocol or research, Country	Study sample	Groups	Aim	Intervention	Role of behavioral science[b]
Barberan-Garcia et al. (2020) *Study protocol* Spain	Moderate-to-high risk lung cancer patients candidates for thoracic surgery Target sample 158 patients in each group	*Intervention:* Standard preoperative management + personalized multimodal prehabilitation program *Control group:* standard care	To evaluate the cost-effectiveness of a multimodal prehabilitation program supported by information and communication technologies in moderate-to-high risk lung cancer patients undergoing thoracic surgery.	Supervised exercise training program + personalized program to promote physical activity (pedometer and mobile app) Nutritional optimization program (personalized dietary counseling + mobile app) Smoking cessation program (cognitive behavioral intervention + pharmacological therapy) Cognitive behavioral therapy (weekly group sessions)	Not explicitly described. Personalized program to promote physical activity included the following: self-monitoring; comparison of behavior with goal; daily motivational message; positive reinforcement once goal is achieved; provision of educational material. BCTs: self-monitoring of behavior, prompts/cues, discrepancy between behavior and goal, prompts/cues, social reward. Aims of cognitive behavioral therapy: reinforce patients "*motivation; to provide coping strategies to manage stress; to foster patients*" engagement for healthy lifestyles. BCT: social support (unspecified)
Brahmbhatt et al. (2020) *Research article* Canada	22 women undergoing breast cancer surgery	Single group received home-based exercise prehabilitation	Examine feasibility and acceptability of home-based prehabilitation prior to breast cancer surgery and exploration of benefits to physical fitness and patient reported outcomes	Individualized exercise prescription including resistance and mobility training 2–3 days per week and aerobic exercise 30–40 min 3–5 times per week	Not explicitly described Participants received an exercise manual and weekly phone calls or emails to support program compliance. BCT: prompts/cues
Loughney et al. (2019) *Research article* Ireland/UK	24 patients: 14 prostate; 10 colorectal cancer	N/A	To assess compliance and adherence of a pragmatic community-based preoperative exercise program and its effect on health-related components of fitness and HRQoL.	MedEx (ExWell Medical), an established medically supervised chronic illness rehabilitation program delivered in a leisure center.	Not explicitly described.
Macleod et al. (2018) *Research article* UK	22 adults with stage I–III colorectal cancer	N/A	To assess the feasibility of delivering and evaluating a lifestyle program for patients with colorectal cancer undergoing potentially curative treatments.	The TreatWELL intervention program targeted smoking, alcohol, physical activity, diet, and weight management. It was delivered in three face-to-face counseling sessions (plus nine phone calls) by lifestyle coaches over three phases (1: presurgery, 2: surgical recovery, and 3: post-treatment recovery).	The behavioral approaches were informed by two main theoretical frameworks: self-regulatory theory and the health action process approach. Informed by behavior change techniques used in previous interventions and the behavior change wheel, a range of evidence-based behavioral techniques were employed to motivate and support lifestyle change. These included motivational interviewing, implementation intentions, self-monitoring, personalized action and coping plans, feedback, and reinforcement. BCTs: social support (unspecified), action planning, self-monitoring of behavior, problem solving, feedback on behavior, and social reward.

(Continued)

TABLE 1 | Continued

Authors, (Year) protocol or research, Country	Study sample	Groups	Aim	Intervention	Role of behavioral science[b]
Ngo-Huang et al. (2019) *Research Article* USA	50 patients with resectable pancreatic adenocarcinoma	N/A, single group	To investigate relationships among physical activity, changes in physical function, and health-related quality of life among patients with pancreatic adenocarcinoma enrolled in a home-based exercise prehabilitation program.	Home-based, multimodal exercise program throughout preoperative therapy. All participants met with a registered dietitian, who provided individualized nutrition recommendations.	Not explicitly described. Participants were called by study staff a minimum of once every 2 weeks to encourage adherence. Participants completed daily exercise logs. BCTs: social support (unspecified), self-monitoring of behavior
van Rooijen et al. (2019a) *Study protocol* The Netherlands, Canada, Denmark, France, Italy, Spain	714 patients undergoing colorectal surgery for cancer	Intervention: 4 weeks of prehabilitation Control group: usual care, no prehabilitation	To determine the impact of multimodal prehabilitation on patients' functional capacity and postoperative complications.	Prehabilitation program composed of four elements: exercise training, nutritional intervention, smoking cessation, and psychological support.	Not explicitly described. Participants were phoned weekly to encourage adherence. BCT: social support (unspecified)
Janssen et al. (2020) *Research article* The Netherlands	627 aged ≥70 years who underwent elective surgery for abdominal aortic aneurysm or colorectal cancer	Intervention ($n = 267$): Prehabilitation program Control ($n = 360$): Usual care	To assess the effects of prehabilitation on 1-year mortality and of postoperative delirium and functional outcomes.	Exercise: Unsupervised, home-based personalized resistance and endurance exercises Nutrition: Dietary advice; vitamin supplements, and protein drinks were provided if needed Prevention of delirium: Supplementary interventions to prevent delirium during admission were provided and advice was given on additional preventive measures.	Not explicitly described.
Barrett-Bernstein et al. (2019) *Research article* Canada	172 patients with nonmetastatic colorectal cancer awaiting curative resection	Prehabilitation group vs. control group: rehabilitation	The primary objectives were to (a) assess differences in functional performance and functional capacity and (b) explore the impact of prehabilitation on functional capacity in individuals with depressive symptoms vs. those without.	Moderate-intensity exercise, nutrition therapy, and stress-reducing strategies.	Not explicitly described
Liu et al. (2020) *Research article* China	73 patients undergoing video-assisted thoracoscopic surgery lobectomy for non-small cell lung cancer.	Prehabilitation group ($n = 37$) vs. Usual clinical care control group ($n = 36$)	To investigate the impact of a short-term, home-based, multimodal prehabilitation program on perioperative functional capacity.	2-week home-based, multimodal intervention program before surgery, including aerobic and resistance exercises, respiratory training, nutrition counseling with whey protein supplementation, and psychological guidance.	Not explicitly described. Patients completed diaries to note activities performed. Patients received an instruction booklet and a physical therapist demonstrated resistance training exercises. BCT: self-monitoring of behavior, demonstration of behavior.
Minnella et al. (2019) *Research article* Canada	70 adult patients scheduled for elective radical cystectomy for nonmetastatic bladder cancer	Prehab group ($n = 35$): multimodal prehabilitation Control group ($n = 35$): standard care	To determine whether a preoperative multimodal intervention is feasible and effective in radical cystectomy.	Preoperative multimodal intervention including aerobic and resistance exercise (individualized, home-based moderate-intensity aerobic and resistance activity), diet therapy, and anxiety-reducing intervention (relaxation techniques).	Not explicitly described. Participants were provided with a logbook to record activities. BCT: self-monitoring of behavior

(Continued)

TABLE 1 | Continued

Authors, (Year) protocol or research, Country	Study sample	Groups	Aim	Intervention	Role of behavioral science[b]
Bousquet-Dion et al. (2018) *Research article* Canada	Patients scheduled for non-metastatic colorectal cancer resection	PREHAB+ ($n = 41$) standard prehabilitation + weekly supervised exercise session vs. REHAB ($n = 39$) standard rehabilitation program	To determine whether a weekly supervised exercise session could provide further benefit to the current prehabilitation program, when comparing to standard post-surgical rehabilitation.	Both multimodal programs were home-based and consisted of moderate intensity aerobic and resistance exercise, nutrition counseling with daily whey protein supplementation and anxiety-reduction strategies.	Not explicitly described. Participants were given a pedometer to encourage daily walking. BCT: self-monitoring of behavior
McCourt et al. (2020) *Study Protocol* UK	60–75 patients with a diagnosis of myeloma	Intervention: exercise prehabilitation Control: usual care	To investigate the feasibility of a physiotherapist-led exercise intervention as an integral part of the myeloma autologous stem cell transplantation pathway at a UK tertiary center.	The exercise intervention comprises of partly supervised physiotherapist-led aerobic and resistance exercise including behavior change techniques to promote change in exercise behavior.	BCTs, to promote adherence to the intervention and behavior change were explicitly described as per the Taxonomy of BCTs and include: goal setting (behavior) problem solving, action planning, review behavior goal, discrepancy between current behavior and goal, feedback on behavior, self-monitoring of behavior, biofeedback, instruction on how to perform a behavior, information about health consequences, information about emotional consequences, demonstration of the behavior, behavioral practice/rehearsal, generalization of target behavior, graded tasks, credible source, pros and cons, adding objects to the environment, verbal persuasion about capability.
Carli et al. (2020) *Research Article* Canada	110 frail patients undergoing colorectal surgery	Prehabilitation group: $n = 55$ Rehabilitation group: $n = 55$	To assess the extent to which a prehabilitation program affects 30-day postoperative complications in frail patients undergoing colorectal cancer resection compared with postoperative rehabilitation.	Multimodal program involving exercise, nutritional, and psychological interventions initiated before (Prehab group) or after (Rehab group) surgery.	Not explicitly described Participants received counseling for smoking and alcohol cessation

[a] *Scientific publications from 2018 onwards only.*

[b] *Role of Behavioral science in terms of: use of theoretical frameworks in intervention development and evaluation; explicit mention of Behavior Change Techniques (BCTs) used in the intervention (where BCTs are not explicitly described as per the Taxonomy of BCTs they have been extracted); inclusion of Behavioral determinants as (outcome) variables, study aims directed at identifying Behavioral mechanisms or effective active ingredients; co-creation of the intervention.*

of involvement and patients who declined participation, to discuss experiences of being invited and their decision-making processes. This will afford important insights into the barriers and facilitators to involvement and enable refinement of future large-scale trials and/or services.

We encourage those designing new trials to include qualitative process evaluations by following published guidance (Moore et al., 2015). Not only does this allow exploration of patient experience, it can shed light on what worked for whom and in what context; vital data to support advancement and implementation of prehabilitation trials and services.

EXAMPLES OF CLINICAL PRACTICE AND BEHAVIORAL SCIENCE INPUT

Existing clinical prehabilitation services typically consist of advice on physical activity, diet, and anxiety or stress reduction techniques. Delivered either in a universal form for example videos or downloadable leaflets on the service provider's website, or personalized patient consultation with one or more members of the prehabilitation team. As seen in the research trial context, the place of program delivery varies. **Table 2** summarizes key characteristics of some ongoing prehabilitation clinical programs. This list is not exhaustive, rather, a snapshot of international provision.

Mirroring the academic literature, most programs do not describe explicit consideration of behavioral science (though absence of evidence is not evidence of absence). However, there is emerging evidence of consideration of optimizing patient motivation and action. For example, the PreHab service in Barcelona, Spain, state patients receive a "motivational interview." The POP program in Montreal, Canada recounts that "a primary goal of the psychological component was to enhance and reinforce patients' motivation to comply with the exercise and nutrition aspects of the intervention." Others refer to 'monitoring progress' and keeping "exercise diaries," activities that support behavior change. However, few services explicitly describe involvement of team members with behavioral science expertise. Many prehabilitation services do however, signpost patients to specialist behavior change services such as alcohol reduction, smoking cessation, or weight management.

ROLE OF SURGERY SCHOOLS

As well as clinical prehabilitation services as described above provision of preoperative education to groups of patients prior to major surgery (surgery school) has become increasingly common. In some clinical services this forms part of the prehabilitation program. A recent national survey undertaken by an author (IFJ) in collaboration with the Manchester prehabilitation leads, identified 32 active and planned surgery schools across the UK and Ireland. Historically these surgery schools focus on education, providing information on what to expect leading up to and following surgery and advisable lifestyle modifications. However, there is little evidence as to whether such schools catalyze behavior change. A recent publication reports 60% of patients attending surgery school in an hospital trust intended to change at least one lifestyle behaviors as a result of attending, and 46% reported doing so (Fecher-Jones et al., 2021). Although these results are encouraging, they highlight the long established "intention-behavior gap" with patients appreciating the potential benefit but without the skills or confidence to act (Rhodes and de Bruijn, 2013). These surgery schools present a unique opportunity to address this. Embedding BCTs that go beyond education and provide patients with skills and knowledge to enact new behaviors could have a powerful impact on many patients. Examples could be supporting realistic goal setting based on current activity levels and personal circumstances (e.g., caring responsibilities, physical environment, and access to facilities) and developing action plans that state specifically when, where and how a behavior will be performed. We therefore recommend professionals developing and delivering surgery schools work with behavioral science colleagues to embed these principles in their services.

DISCUSSION

Evidence of the benefits of cancer prehabilitation has burgeoned in the last few years and with it emerging clinical practices. There is increasing recognition of the importance of including strategies to enhance motivation and maximize compliance with programs. This is particularly important as programs move away from highly structured and supervised clinical environments to home and community-based settings. We encourage those developing new trials and services to collaborate with the behavioral science community to strengthen these efforts.

The key to successful behavior change interventions, like any other, is to understand the underlying determinants (in this case, that drive behavior) and what strategies are useful to influence them. Behavioral scientists can help address this; identifying underlying processes that impact on uptake and adherence and support the evaluation and refinement of these programs to maximize satisfaction and identify the most effective BCTs. Furthermore, working with end-users and iterative improvements based on their feedback is essential if programs are to be truly patient-centered and engagement maximized. Optimizing self-efficacy to engage in programs, as well as ensuring they are relevant to each patient are of notable importance.

It is also important to recognize credible concerns that complex interventions such as prehabilitation may inadvertently increase disparities between patients who do and do not engage. The demographic profile of cohorts involved in clinical trials in this area tend to over represent white, relatively young and well-educated populations. There is also a suggestion that clinicians can act as gatekeepers, choosing not to refer, for example, frail older adults to prehabilitation services or trials due to concerns that they may not be suitable or safe for these individuals. Arguably, these patients have the most to gain but may

TABLE 2 | Clinical prehabilitation services and behavioral science input.

Location	Name	Brief description of service	Components	Evidence of behavioral science input
Hospital Clinic Barcelona, Spain	PreHab	Supervised exercise, a mobile app-based personalized program to promote physical activity, dietary counseling and mindfulness sessions. In addition, psychological counseling is offered through specialist services as needed (Barberan-Garcia et al., 2020; Carli et al., 2020; PreHab, 2020)[a]	Physical, Nutritional, and Psychological (mindfulness)	Motivational interviewing is used as an underpinning delivery modality. The mobile app used to promote physical activity includes several behavior change strategies for example goal setting, self-monitoring, motivational tips, referral to smoking cessation services and alcohol services (Barberan-Garcia et al., 2020)
Manchester, UK	Prehab4Cancer	The service is based on ERAS+ (Prehab4Cancer, 2020) and includes Surgery School, and advice on how to increase daily exercise and perform breathing exercises, how to improve diet, advice on alcohol intake, and smoking reduction and management of psychological distress (Moore et al., 2017, 2020)	Physical, Nutritional, and Psychological	Not explicitly described The exercise component is delivered in community leisure centers aiming to induce long-term lifestyle behavioral change. Authors state inclusion of surgery school that uses "behavior change methodology" p3 (Moore et al., 2020), no details provided.
Montreal, Canada (Montreal General Hospital/McGill University)	Perioperative program (POP)	Home-based individualized exercise and diet prescription and teaching/practicing relaxation techniques. Supervised exercise is provided as needed. Smoking cessation support is included as needed (Barrett-Bernstein et al., 2019; Perioperative Program, 2020)[a]	Physical, Nutritional, and Psychological	Not explicitly described A primary goal of the psychological component was to "enhance and reinforce patients' motivation to comply with the exercise and nutrition aspects of the intervention" (Barrett-Bernstein et al., 2019)
Victoria, Australia (Peter MacCallum Cancer Centre)	Fit4Surgery	Personalized home-based and/or supervised gym exercise program, prescription of respiratory exercises, dietary advice, psychological support as needed and invitation to Surgery School (Peter MacCallum Cancer Centre, 2020; Tang et al., 2020)[a]	Physical, Nutritional, and Psychological	Not explicitly described The service development was informed by a patient experience-based co-design approach aiming to increase patient engagement (Tang et al., 2020). The psychological intervention includes discussions about ways to maintain motivation to carry out the activities throughout the prehabilitation period (Peter MacCallum Cancer Centre, 2020)
St Georges Hospital, London, UK	Get Set 4 Surgery	The service includes psychoeducation in the form of Surgery School (group psychoeducation) and access to the Macmillan Move More physical activity program (St George's University Hospital NHS Foundation Trust, 2020)	Physical, Psychoeducational	Not explicitly described
Imperial College Hospital, London, UK	PREPARE	A personalized exercise program and diet prescription, complemented by advice on respiratory exercises and psychological support as included in the service (Doganay and Moorthy, 2019; Imperial College Healthcare NHS Trust, 2020)	Physical, Nutritional, and Psychological	Not explicitly described The program includes use of exercise diaries for patients to monitor their progress and weekly review of progress by telephone contact from the exercise specialist. Progress with dietary changes is monitored and advice is adjusted as needed. The focus of psychological support is on improving self-efficacy. Behavior change support such as establishing short and long-term goals, providing feedback and connecting patients for peer support are employed (Doganay and Moorthy, 2019)

(Continued)

TABLE 2 | Continued

Location	Name	Brief description of service	Components	Evidence of behavioral science input
Maxima Medical Centre, Eindhoven, The Netherlands		Combination of fitness and strength training, nutritional support, psychological help and, if necessary, a smoking cessation process (van Rooijen et al., 2019b; Maxima Medical Centre, 2020)[b]	Physical, Nutritional, Psychological, and Smoking cessation	Not explicitly described The pilot RCT study for the multi-modal prehabilitation program included weekly phone calls with a specialist nurse to increase adherence to the program and included discussing coping mechanisms and encouraging "training perseverance" (p. 891). "Coaching" (p. 890) by a psychologist was also included although there are no details of what this entailed (van Rooijen et al., 2019b). It is unclear whether these elements were implemented in the service
Medway NHS Foundation Trust, UK	Kent and Medway Prehab	Personalized face-to-face or virtual (video/phone) exercise sessions, dietary and psychological support (Kent Medway, 2020; Wu et al., 2020)[a]	Physical, Nutritional, and Psychological	Not explicitly described Referral to smoking cessation and alcohol reduction services. The program is individualized taking into account people's preferences and values. Community setting makes service more accessible and increases the possibility of social support by family's and friends' (Wu et al., 2020)
South Tees, UK	PREP-WELL	Two supervised exercise sessions and home-based training. Respiratory exercise for those deemed high risk, dietary advice, nutrition support as appropriate and referral for mindfulness training or psychological counseling as needed (South Tees Hospital NHS Foundation Trust, 2020; Tew et al., 2020)[a]	Physical, Nutritional	Not explicitly described Referral to smoking cessation services, alcohol reduction services and psychological services

[a] *The referenced paper describes either a research study or a service improvement pilot that is a variant of the intervention in the service. The description of the intervention is based on the details available on public service websites. All efforts have been made to identify papers describing the closest variant of the published service.* [b] *It is unclear from the available public information whether all elements of the pilot were implemented in the service.*

also need additional support to engage and adhere. It is therefore imperative that we strive collectively to increase inclusivity, working with all stakeholders and engaging with under-represented groups.

The prehabilitation community must focus on person-centered intervention development that enables patients to feel engaged and empowered. With more researchers and practitioners forging new collaborations with behavioral science colleagues to embed these principles in the development, optimization, and evaluation of new programs, we can deliver evidence and needs-based services that stand to provide enormous benefits to people with cancer.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

CG drafted the manuscript. All authors (KB, SD, IF-J, MH, JV-S, CS, and CG) provided substantial intellectual contributions, reviewed, edited, and approved the final manuscripts.

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METHODS
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A Pragmatic Non-Randomized Trial of Prehabilitation Prior to Cancer Surgery: Study Protocol and COVID-19-Related Adaptations

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Background: Experimental data highlight the potential benefits and health system cost savings related to surgical prehabilitation; however, adequately powered randomized controlled trial (RCT) data remain nascent. Emerging prehabilitation services may be informed by early RCT data but can be limited in informing real-world program development. Pragmatic trials emphasize external validity and generalizability to understand and advise intervention development and implementation in clinical settings. This paper presents the methodology of a pragmatic prehabilitation trial to complement emerging phase III clinical trials and inform implementation strategies.

Methods: This is a pilot pragmatic clinical trial conducted in a large academic hospital in Toronto, Ontario, Canada to assess feasibility of clinical implementation and derive estimates of effectiveness. Feasibility data include program referral rates, enrolment and attrition, intervention adherence and safety, participant satisfaction, and barriers and facilitators to programming. The study aims to receive 150 eligible referrals for adult, English-speaking, preoperative oncology patients with an identified indication for prehabilitation (*e.g.*, frailty, deconditioning, malnutrition, psychological distress). Study participants undergo a baseline assessment and shared-decision making regarding the intervention setting: either facility-based prehabilitation or home-based prehabilitation. In both scenarios, participants receive an individualized exercise prescription, stress-reduction psychological support, nutrition counseling, and protein supplementation, and if appropriate, smoking cessation program referrals. Secondary objectives include estimating intervention effects at the week prior to surgery and 30 and 90 days postoperatively. Outcomes include surgical complications, postoperative length of stay,

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mortality, hospital readmissions, physical fitness, psychological well-being, and quality of life. Data from participants who decline the intervention but consent for research-related access to health records will serve as comparators. The COVID-19 pandemic required the introduction of a 'virtual program' using only telephone or internet-based communication for screening, assessments, or intervention was introduced.

Conclusion: This pragmatic trial will provide evidence on the feasibility and viability of prehabilitation services delivered under usual clinical conditions. Study amendments due to the COVID-19 pandemic are presented as strategies to maintain prehabilitation research and services to potentially mitigate the consequences of extended surgery wait times.

Keywords: prehabilitation, cancer, pragmatic trial, cancer surgery, health quality, implementation science, feasibility

INTRODUCTION

Surgery is a highly prevalent primary treatment for localized tumors. Patients undergoing cancer surgery are at risk for surgery-related morbidity and mortality. For example, the rates of mortality and significant complications within 30 days of major abdominal cancer surgery are 4 and 50%, respectively (1). Numerous health-related quality of life (HRQOL) consequences are also common after oncologic surgery and may persist for an indefinite period (2). Frail cancer patients are especially at risk for surgery-related complications that lead to morbidity and mortality. Rockwood et al. define frailty as a multidimensional syndrome of diminished reserves that lead to increased vulnerability (3). A meta-analysis assessing the relationship between frailty and adverse outcomes across all surgical procedures found that frailty was associated with increased risk of surgical and perioperative complications, as well as readmission, postoperative discharge to skilled care, and mortality (4). Many of these adverse surgical outcomes have shown to be related to prolonged pain (5) and functional disability (6–9), as well as greater healthcare costs (10–12). Accordingly, identifying and mitigating frailty in cancer patients and other at-risk groups (*e.g.*, geriatric) are recommended to appropriately manage surgical risk (13, 14).

There are over 70 frailty assessments aimed at identifying or measuring the extent of frailty, many of which are multidimensional and include assessments of physical and cognitive function, nutritional status, comorbidities, and other factors that might affect the patient's physiologic reserve or tolerance for surgery (13, 15). Clinicians' impressions of frailty *via* bedside assessments have also demonstrated strong predictive capacity for identifying patients at risk of significant surgical morbidity or mortality (16). One strategy to manage surgical risk following identification of vulnerability is prehabilitation. Prehabilitation refers to assessments and interventions initiated prior to treatment to create physiologic and psychosocial buffers that can be protective against anticipated deconditioning, complications, and chronic morbidity that occur as a result of the treatment itself (17, 18). Contemporary prehabilitation is multimodal, often including a combination of exercise, enhanced nutrition, stress management, smoking cessation, and medical optimization strategies—strategies that are also commonly used to reduce frailty.

Systematic reviews and meta-analyses of prehabilitation prior to cancer surgery have reported encouraging findings, including improved physical fitness, length of stay, surgical complication rates, and HRQOL (19–24). In recent years, growing attention has been paid to patients who are frail, higher risk, and/or vulnerable to surgical complications, and thus likely to benefit most (25–27). For example, Barberan-Garcia et al. (26) conducted an RCT of prehabilitation in 174 'high-risk' patients defined as older than 70 years and/or an American Society of Anesthesiologists score of III/IV, over half of whom were oncology patients. The intervention was feasible and safe, and prehabilitation reduced postoperative complications by half compared to the control group. Importantly, in a follow-up economic analysis, their intervention cost 389 Euro and yielded a six-fold reduction in risk of hospital readmissions at 30 days, collectively yielding a potential cost savings of up to approximately 800 Euro per patient (28). Aligned with these emerging data are implementation recommendations that include triaging strategies that prioritize prehabilitation for 'at-risk' or 'frail' patients for whom the benefits and cost effectiveness are likely to be greatest (29–31).

As evidence regarding the efficacy and potential healthcare savings for prehabilitation in cancer surgery continues to mount, consideration for clinical care pathways, delivery strategies, and required infrastructure and personnel are important pragmatic considerations for potential implementation. Data in these areas are lacking, spurring calls for pragmatic effectiveness trials of prehabilitation models of care (32). Pragmatic trials complement RCTs, the latter of which are considered the gold standard for assessing efficacy and causality, but whose methodological principles emphasize internal validity, often at the expense of generalizability to clinical practice. As such, public health and clinical research initiatives have increasingly sought to generate parallel 'practice-based evidence' to advise the development of intervention designs that can be applied in the real-world

setting (33). Practice-based evidence can be derived from implementation science research methods, such as pragmatic trials, that assess intervention effectiveness in real-world settings and provide insight into the system's capacity and preparatory needs for dissemination or scalability (34). The blending of experimental and implementation evidence has been suggested to target both internal and external validity and can offer important insight into implementation that cannot be well ascertained in conventional RCTs alone (34, 35).

To complement the growing RCT evidence, we designed a pragmatic trial of prehabilitation for people undergoing cancer surgery to advance the understanding of health professional engagement, delivery modality preference, and other insights related to the strategies, facilitators, and barriers of prehabilitation program implementation. Hereafter, we provide the trial protocol including adaptations related to the COVID-19 pandemic.

STUDY OBJECTIVES

The primary objective of this study is to assess the feasibility of delivering a multimodal surgical prehabilitation service to surgical oncology patients. The secondary objectives are to explore the effectiveness of the program using clinical, physical, and patient-reported outcome measures. The specific research questions guiding this study design are listed in **Box 1**.

METHODS

Design

This is a pragmatic, preference-based, non-blinded, non-randomized trial to assess the feasibility and estimates of effectiveness of a clinically integrated, multimodal prehabilitation program for frail surgical oncology patients in an urban academic health center in Toronto, Ontario, Canada. Participant flow throughout the study is presented in **Figure 1**. The initial study protocol and subsequent amendments related to the COVID-19 pandemic have been approved by the University Health Network research ethics board.

BOX 1. Study Research Questions.

Feasibility Research Questions:

RQ1a: How many referrals for prehabilitation will be received and what are the identified indications for prehabilitation?

RQ1b: Does a surgeon's bedside assessment of frailty (as indicated by referral and reason for referral) correspond with established frailty indices?

RQ1c: What percentage of referred patients participate in prehabilitation?

RQ1d: What are the demographic and medical characteristics of patients who are referred to for prehabilitation?

RQ1e: What factors contribute to participants choosing either FBP or HBP?

RQ1f: What is the 'prehabilitation window' for participants (i.e., time from treatment decision to surgery)?

RQ1g: What is the adherence rate to the multimodal components defined by the prehabilitation protocols?

RQ1h: Is prehabilitation safe within a clinical model of care (i.e., number and nature of adverse events)?

RQ1i: What are the barriers and facilitators to prehabilitation?

RQ1j: What are the various costs and potential cost savings associated prehabilitation?

Exploratory Effectiveness Research Questions:

RQ2a: What changes in clinically relevant outcomes do participants experience by the week prior to surgery and up to 90 days after surgery?

RQ2b: Compared to usual care, what effect does prehabilitation have on peri- and postoperative outcomes (up to 90 days after surgery)?

(RQ, Research Question)

Participants

Consistent with pragmatic trial methodology (34), broad inclusion criteria for study participation are employed for generalizability to the heterogeneity of patients that may be referred to a clinical service. Eligible patients for this study are: i) scheduled for cancer-related surgery; ii) 18 years of age or older; iii) fluent in English; and iv) referred by a health professional with an indication for prehabilitation (*e.g.*, higher-than-average risk candidate; marginal candidate for surgery due to perceived limited physiologic reserve; frail; deconditioned; 'other' with explanation).

Sample Size

A period of trial enrolment, rather than target sample size, was selected to inform expected rates of referral for a clinical service. The trial anticipates receiving 150 referrals for prehabilitation over 12 months. We estimate that one third of all referred patients will decline the intervention but will consent to making their hospital records related to their pending cancer surgery available for research (hereafter referred to as 'usual care' participants).

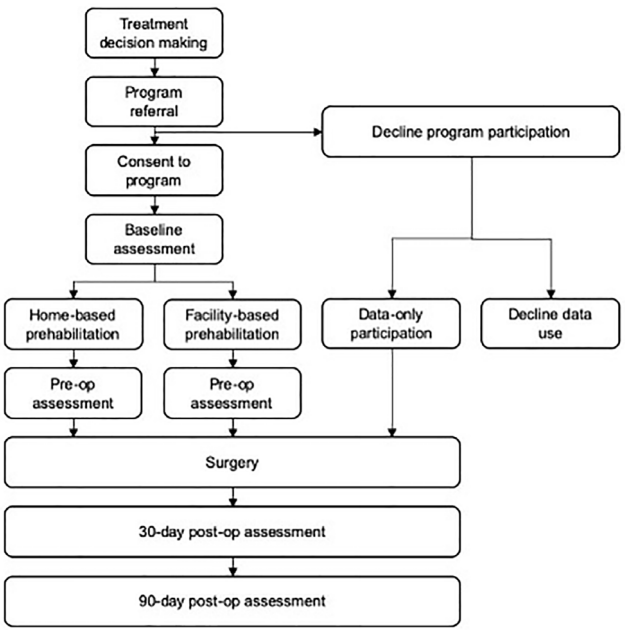

FIGURE 1 | Participant flow.

Outreach and Enrolment

A patient referral strategy for enrolment is adopted to model conventional clinical programming. To inform institutional stakeholders of the research project (*e.g.*, physicians and surgeons, physician assistants, nurses, and administrative assistants), a campaign of presentations, meetings, and emails pertaining to the study is conducted across surgical teams, in multidisciplinary rounds, and ambulatory clinics. Clinical teams receive information on the study's objectives and methodology, including information on how to refer patients to the study, the referral form, and a prehabilitation program handout to review and distribute to patients. Clinicians are advised to introduce the study to patients whom they feel may be appropriate candidates for surgical prehabilitation at or near the time of treatment decision-making or during other medical visits associated with surgical planning (*e.g.*, comprehensive geriatric assessment). If the patient is interested in learning more or participating in the program, clinicians are advised to fax the study referral to the research team who subsequently contact the patient to discuss the study and obtain informed consent from agreeable and eligible patients (including usual care participants).

Health History Interview and Baseline Assessment

At baseline, the research coordinator conducts a health history interview to ascertain information about their cancer diagnosis, planned surgery and related treatments (*e.g.*, neoadjuvant therapy), other injuries, illnesses and their associated treatments, previous experience with physical activity and exercise, nutrition and psychological stress. The health history interview aids in individualization of the prehabilitation programming and is supported by the following measures: the Charlson Comorbidity Index (CCI) (36); the Edmonton Frail Scale (EFS) (37); the Duke Activity Status Index (DASI) (38); the Canadian Nutrition Screening Tool (CNST) (39); the Perceived Stress Scale (PSS) (40), and the Godin Leisure-Time Exercise Questionnaire (GLTEQ) (41, 42). Finally, a 3-day food record is also used to quantify nutritional intake to aid dietary assessment and recommendations from the dietitian.

Peak aerobic fitness (VO_{2peak}) is measured *via* a cardiopulmonary exercise test (CPET) using a cycle ergometer-based ramp protocol (43, 44) to determine safety and exercise parameters for participants engaging in high-intensity interval training (HIIT). Gas exchange is measured by indirect calorimetry *via* metabolic cart (TrueOne 2400, Parvo Medics, Sandy, UT, USA) and heart rate and rhythm are monitored continuously *via* 12-lead ECG (CASE, General Electric Healthcare, Chicago, IL, USA). Blood pressure, respiratory rate, and rating of perceived exertion are measured at the start of the test and routinely throughout.

Prehabilitation Program

To accommodate individual factors that support program participation, prehabilitation is offered as either a facility-based or home-based intervention. Facility and home-based intervention delivery offer unique advantages and disadvantages that may relate to program participation and outcomes which are of particular interest to this study. In facility-based programming, health professional supervision can facilitate expedient adaptation and progression of the intervention to optimize patient safety and intervention efficacy (45). The disadvantages of facility-based programming relate to the accessibility of the facility (*e.g.*, distance, traffic, cost of fuel/parking, timing of facility-hours) and the general lack of program availability due to the institutional cost of intervention delivery (46, 47). Alternatively, home-based programs are less resource intensive for institutions to deliver and may impose fewer barriers to participant engagement which adds flexibility to accommodate schedules. A drawback of home-based programming is the absence of direct supervision which may limit intervention dose delivery, and consequently intervention efficacy, with the added reliance on potentially biased self-report measures to capture adherence and progress (48, 49).

In the present study, we sought to examine trends in delivery mode preference and participation and offered two streams of prehabilitation programming: home-based prehabilitation (HBP) and facility-based prehabilitation (FBP). To support patients in determining their preferred or optimal intervention setting, the research coordinator (who is also a health professional) engages in a shared decision-making conversation during the baseline assessment using the 'choice, option, decision talk' framework (50). Participants then continue with the baseline assessment oriented towards either HBP or FBP. Each intervention arm is similar in terms of intervention content (described further below) and primarily differs by the location of participation, where HBP participants engage with the intervention exclusively at home or their community and are remotely supported/counseled by telephone, whereas FBP participants engage in intervention *via* session occurring at the facility (*i.e.*, hospital) and at their home or community.

Exercise

Each participant's exercise prescription is developed and delivered by a kinesiologist and individualized to the results and observations obtained during the baseline assessment. Participants in both groups receive a moderate intensity aerobic and resistance training prescription to be completed 3–5 times per week for 60 min per session. Exercises specific to the anticipated locoregional impairments associated with the pending surgery are also prescribed for FBP and HBP participants to be completed independently. Participants in FBP are encouraged to attend two facility-based sessions per week where the aerobic training includes HIIT using the 10 × 1 protocol (51), and on such days, resistance training using the facility's equipment is commenced after a 10 min rest period. All home- or community-based exercise sessions are supported with the provision of a stability ball, resistance bands, and a manual free of charge, and are intended to be completed independently (*i.e.*, unsupervised). Prior to initiating the exercise program, all exercises are instructed and demonstrated in the prehabilitation program facility where participants have an opportunity to practice and receive feedback/corrections or alternate exercises.

The kinesiologist communicates weekly with participants by telephone to support program compliance, record adherence, appropriate progression, and to address any barriers to exercise that may prevent participation. Details of the aerobic and resistance training programs, as well as the locoregional impairment-based exercises are provided in **Tables 1** and **2**, respectively.

Nutrition

A dietitian conducts an initial individualized nutrition assessment and counseling session within the first week of prehabilitation and again in the week prior to surgery. Each consultation is ~60 min and includes a review of the patient's nutritional and weight history (including information from the 3-day diet record) and conversation regarding strategies to help

TABLE 1 | Exercise-based Total Body Prehabilitation.

	Home-based prehabilitation (HBP)	Facility-based prehabilitation (FBP)
Frequency	3–5 sessions per week (plus additional sessions for locoregional exercises as indicated)	
Intensity—Aerobic	MICT at 40–70% HRR or an RPE of 4–7/10	Home-based sessions are as per HBP. Facility-based sessions (twice weekly) employ the 10 × 1 HIIT protocol (10 cycles of exercise and recovery intervals, each interval is 1 min). During the first week, exercise intervals are 70–80% VO_{2peak} in session 1 and 75–85% VO_{2peak} in session 2 with recovery interval at a target an intensity of ≤50% VO_{2peak}. In the second week and up to date of surgery, the exercise interval intensity target is set to 85–95% VO_{2peak}.
Intensity—Resistance	2–3 sets of 8–12 repetitions at approximately 12–15 repetition maximum	
Time (duration)	Exercise sessions are intended to incorporate 25 min of aerobic and resistance training each plus a 5-min warm-up and cool-down. The total duration of training is intended to take approximately 60 min, but sessions may be divided into shorter bouts as needed.	
Type—Aerobic	The default modality of home-based training is brisk walking, or a low-intensity aerobic step class video developed and previously used by our team. Additional modalities of aerobic exercise may be used based upon the participants access (*e.g.*, attendance to a local fitness facility)	Home-based sessions as per HBP. Facility-based HIIT sessions use a treadmill or stationary cycle.
Type—Resistance	exercises targeting major muscle groups of the body (*e.g.*, shoulders, chest, upper/lower back, core, upper/lower legs).	
Progression—Aerobic	Progression of MICT will increase from the lower limit of the range (*e.g.*, 40% HRR) towards the upper limit of the range (*e.g.*, 70% HRR), and if required an increase in duration is implemented to progress the total aerobic training volume. Progression of HIIT is as per the familiarization and standard protocol described above, as well as progressing from the lower end of the standard range (85% VO_{2peak}) to the upper limit (*e.g.*, 95% VO_{2peak})	
Progression—Resistance	Progression in resistance intensity occurs when 15 repetitions of a given exercise can be completed with only mild exertion.	

HIIT, High intensity interval training; HRR, heart rate reserve; MICT, moderate intensity continuous training; VO_{2peak}, peak oxygen uptake (as determined during baseline cardiopulmonary exercise test).

TABLE 2 | Locoregional/Targeted Preoperative Exercises.

Surgery	Description & Rationale	Training modalities
Abdo-thoracic (*e.g.*, lung resection, upper abdominal)	Exercises of the inspiratory muscles and diaphragm aim to increase the endurance, strength and performance of the inspiratory tissues. This has been shown to reduce pulmonary complications from abdo-thoracic surgery (52, 53).	Deep diaphragmatic breathing and inspiratory muscle training (IMT) with a threshold-loading device and nose plug (Threshold IMT, Respironics, Inc., Murrysville, PA, USA) Frequency: 5–7 times per week; Intensity: 4-7/10 on RPE scale. Duration: 15–30 minutes.
Urological (*e.g.*, prostatectomy, hysterectomy)	Training of the pubococcygeus, iliococcygeus, coccygeus, and puborectalis muscles, collectively referred to as the pelvic floor muscle exercise training has shown to reduce time to continence as well as the severity of incontinence postoperatively (19, 54).	Pelvic floor muscle exercises (contract and hold or 5–10 s) consistent with institutional strategies for radical prostatectomy rehabilitation Frequency: three sessions per day, every day; Intensity: maximal contraction for 10–20 repetition; Duration: ~5 min per session.
Breast (*e.g.*, lumpectomy, mastectomy)	Exercises targeting the upper quadrant and core are associated with early recovery of morbidity associated with resection and reconstruction (55).	Stretching and general strengthening of the shoulder, chest, and mid/upper back muscles consistent with institutional rehabilitation strategies for breast cancer surgery. Stretching is recommended daily and strength is incorporated into general conditioning protocol (described in **Table 1**).
Head and neck	Exercises of the pharyngeal muscles involved in speech and swallowing have primarily been used prior and during radiation and chemoradiation (56). Improvements in dysphagia and quality of life have been reported in patients undergoing treatment for head and neck cancer (57, 58).	Respiratory-swallowing coordination, postural exercises, tongue, jaw, and neck muscle strengthening (*e.g.*, supraglottic swallow, Masako technique). These comprise five swallowing exercises performed three sessions per day. Frequency: Daily; Intensity: not applicable; Duration: approximately 5 min per session

RPE, rating of perceived exertion.

the patient optimize or enhance the nutritional quality of the diet aligned with Canada's Food Guide (59). Additionally, counseling regarding the maintenance of a healthy weight, minimizing excessive weight gain or weight loss, and addressing any nutrition-related questions or concerns specific to the pre and postoperative period is provided. To maintain protein sufficiency for exercise and prevent catabolism associated with the perioperative experience, participants are provided with 26 g packets of whey protein isolate, free of charge, to be consumed daily mixed in a beverage or food (ISOlution, Enhanced Medical Nutrition, Toronto, ON, CA) (60, 61). Participants are encouraged to contact the dietitian as needed for on-going support.

Stress Management and Behavioral Support

Within one week of initiating prehabilitation, a psychologist delivers a ~60-min psychoeducation session that focuses on stress management *via* relaxation, mindfulness, goal setting, and strategies to overcoming barriers to practice. In the week prior to surgery, participants are offered a second 60-min consultation with the psychologist to review their stress management experiences and provide further support for the acute perioperative period. To help participants with daily stress management practice, publicly available links to written and audio-based materials describing mindfulness, progressive muscle relaxation, deep breathing, and visualization are also provided.

Smoking Cessation

Participants that smoke are provided with information on the Canadian Cancer Society's Smoker's Helpline (www.smokershelpline.ca) for online programming and tools, as well as one-on-one counseling support. Smokers are also advised to speak to their local pharmacist and/or family doctor who can provide additional counseling, including education on the use of nicotine replacement therapy.

Study Outcomes

Participant data to assess feasibility and derive estimates of effect are collected from the participants' referrals, at the baseline assessment, within 1 week prior to surgery, and at 30 and 90 days postoperatively.

The total number of referrals and the rate at which they are received (per month) will be reported. To characterize the patients referred to the program, the following are collected from all referral forms (including usual care participants and those who decline research): referring surgical service; reason for referral; frailty level (*via* the Clinical Frailty Scale (3), embedded into the referral); cancer type; indicated surgery; referring healthcare practitioner type (*i.e.* physician, surgeon, clinic nurse, *etc.*), and participant demographics (age, sex, and general geographic location). The enrolment rate will be calculated as [# of enrolled participants]/[# of referred participants]. The frequency and reasons for declining participation in the study, declining prehabilitation (*i.e.*, usual care participants), and drop-out will be reported and compared using descriptive statistics of demographic and referral data.

Given the importance of scheduling and timing for prehabilitation relative to the date of surgery, several relevant time periods will be reported. The time from program referral to the date of surgery will be reported and is referred to as the 'prehabilitation window'. We will also report the total preoperative period (time between consent for surgery and date of surgery) and prehabilitation duration (time from baseline assessment to surgery).

Reporting of the exercise prescription parameters and adherence to the programming will follow the Consensus on Exercise Reporting Template (62). Adherence to home and facility-based exercise sessions are recorded *via* attendance and standardized logbooks capturing training activity completed by the research coordinator. Adherence to stress management, nutrition plan, protein consumption, and utilization of smoking cessation tools (as required) is recorded weekly using a logbook within the participant manuals. Healthy eating practices advised by the dietitian are also assessed by a 3-day diet record in the week prior to surgery. Safety or adverse events related to prehabilitation are discussed during weekly communication between the participants and the research coordinator. Reporting and grading of adverse events will follow the Common Terminology Criteria for Adverse Events version 5.0 (63).

Estimates of program effectiveness are derived from a combination of patient-reported and functional performance measures, as well as clinical information from the medical record at each of the study timepoints. Aerobic functional capacity is measured using the Six-Minute Walk Test (6MWT) (64) and musculoskeletal functional capacity is assessed *via* grip strength using an isometric dynamometry (Jamar, Sammons Preston, Bolingbrook, IL, U.S.A.) according to established protocols (44). Body mass (kilograms) and height (meters) are measured using standardized procedures and are used to calculate body mass index (BMI, kg/m^2). Body fat percentage, fat and fat free mass, impedance, resistance, and phase angle are recorded are measured *via* bioelectrical impedance analysis (mBCA 514, Seca, Hamburg, Germany) (65). HRQOL is measured using the 12-item Short Form Health Survey (SF-12) (66, 67) and the EuroQol 5 Dimensions 5 Levels (EQ5D-5L) (68) The Patient Health Questionnaire (PHQ-9) is used to assess depression (69). The EFS, PSS, and GLTEQ are also re-administered at each follow-up timepoint. Postoperative length of stay in number of days (including any readmissions) is recorded from the medical record. Complications, including mortality, are reported according to the Clavien-Dindo classification (70). All health events that require readmission will also be documented. Complication and health event data are extracted from the medical record at the 30^{th} and 90^{th} postoperative day for each participant.

Economic evaluation will be conducted from the perspectives of the individual and the hospital. Cost for an individual prehabilitation participant will be calculated on two fundamental components: the quantity of resources consumed and the unit cost of those resources related to prehabilitation. The EQ5D-5L will be used for the cost–effectiveness analysis as the health effect to determine the quality-adjusted life years (QALY) for the 90-day follow-up time period. The calculated participant costing and

QALY will be used to determine the incremental cost–effective ratio (ICER). ICER will be calculated as a ratio of the difference in patient costing and the difference in QALY between FBP and HBP [ICER = $(cost_{FBP} - cost_{HBP})/(QALY_{FBP} - QALY_{HBP})$]. This will be calculated for both the program (measured cost for delivery of FBP and HBP) and patient perspective. Patient-perspective costing is measured by a patient-reported cost-diary that includes: direct healthcare cost (impact of the interventions on the use of healthcare services, such as visits to the general practice, specialist care, prescribed medication); direct non-healthcare costs (cost incurred by the patient and the family, such as cost of over-the-counter medication, cost of health activities, hours of paid and unpaid household help, transportation, and value of other out-of-pocket expenses, with specifics on exercise-related expenses); and indirect costs (value of productivity lost due to illness-related absence, including number of days absent from work, days lost from housekeeping, and other daily activities). A cost–impact from the perspective of the hospital will be conducted based on surgery-related hospital length of stay, readmission frequency, and length of stay of readmission(s) will be used to determine cost differences between those that participate in prehabilitation versus usual care participants. Cost impact will be estimated by applying the unit cost of an inpatient hospital day to the differences for participants that enrolled in prehabilitation and those that did not. Data from the Canadian Institute for Health Information on average cost of hospital stay will be used for the respective year.

In the second year of the study, prehabilitation participants will be asked to participate in semi-structured interviews conducted by telephone or in-person. The purpose of the semi-structured interviews is to capture insights about participant satisfaction, as well as the facilitators and barriers to prehabilitation engagement. To reach saturation for identifying meta-themes within a heterogenous population, a purposive sample of at least 15 participants per study arm will be sought to identify prevalent and salient themes related to study experiences. Qualitative content analysis will be conducted to identify barriers and facilitators for prehabilitation participation and engagement will be conducted using semi-structured interviews.

Analytic Plan

The analytic plan is described for prehabilitation implementation feasibility outcomes and exploratory analyses of prehabilitation effects. In line with comparative effectiveness research, presentation of confidence intervals will be emphasized for the purpose of accurately reflecting the actual data as well as directly addressing the uncertainty of the data. All quantitative analyses will be conducted in R (R Foundation for Statistical Computing, Vienna, Austria) and an alpha of.05 will be used.

Demographic and disease characteristics of all referred patients, as well as prehabilitation and usual care participants' will be summarized with appropriate parametric and non-parametric statistics. Reasons for ineligibility, declined participation in the study or intervention, as well as reasons for choosing FBP or HBP will be tallied. Group comparisons for referral information (surgical service, type of cancer, type of surgery, age, sex, and geographic location) will be assessed by one-way analysis of variance (ANOVA) for continuous and Chi-square test for categorical variables and described across FBP, HBP, usual care, and participants who decline participation. Baseline demographic and disease-related variables will be compared between study participants (FBP, HBP and usual care) ***via*** one-way ANOVA for continuous variables and Chi-square test for categorical variables.

Adherence to the interventions will be summarized dichotomously as meeting or not meeting the prescribed intervention components across each domain (exercise, nutrition, psychology, and smoking cessation). Reasons for deviations will be thematically categorized and summarized by frequency and percentage. Retention rates will be calculated as a total percentage of dropouts at the presurgical time point to the total participants enrolled for FBP and HBP. Reasons for dropout will be summarized using frequencies and percentage for each prehabilitation arm. Reported safety or adverse events will be summarized using frequencies and percentage for each group.

To provide an estimate of effect of HBP and FBP, point estimates and 95% confidence intervals will be calculated for changes in physical fitness, patient-reported outcomes from baseline to the 90-day time point using linear mixed effect models. Estimated mean hospital length of stay for HBP, FBP, and usual care, as well as between-group differences, will also be conducted using a linear mixed effect model. Incidence rate ratios and estimating rate differences for postoperative complication, readmission, and morbidity for prehabilitation in reference to usual care at 30 and 90 days after surgery will be made using Poisson regression. Tukey HSD will be used to adjust for multiple comparisons. In the presence of outliers, bootstrapping regression coefficient methodology will be done to obtain valid confidence intervals.

Semi-structured interviews regarding participant satisfaction as well as facilitators and barriers with the intervention will be transcribed verbatim and undergo qualitative content analysis. Initial transcript sample readings will be independently done by two researchers. Preliminary themes will be noted, and differences will be resolved, and duplications will be eliminated. Themes and content will be analyzed descriptively. Coding, linking, and retrieving the qualitative data will be conducted using NVivo software (QSR International, Melbourne, AUS).

Protocol Adaptations in Response to the COVID-19 Pandemic

COVID-19 containment measures have reduced elective surgery volumes around the world. Reduced surgical capacity has led to longer wait times for elective procedures and patients are experiencing declining physiological and psychosocial health in the unsettling context of social distancing, community service closures, and economic hardship. This loss in health is likely to be most profound for older patients and those with complex medical needs. Consequently, the extended waiting time is likely to negatively impact disease progression and surgical tolerance that may lead to higher rates of adverse surgical outcomes, ultimately compounding COVID-19-related health system strain. Given that prehabilitation may play an important role in mitigating the deterioration of health and well-being during

extended surgical wait times, this study implemented several amendments to accommodate pandemic-related restrictions and barriers to healthcare in an attempt to maintain the opportunity for prehabilitation participation for planned but unscheduled, or delayed, cancer surgery. A summary of the amendments approved by the institutional ethics board is provided in **Box 2**.

DISCUSSION

As the evidence supporting prehabilitation for cancer surgery grows, questions about if and how it may be integrated into standard of care have followed. This protocol describes a study aimed at advancing implementation evidence to complement ongoing RCTs that target efficacy outcomes. Collectively, these will inform clinicians and researchers about the value and feasibility of clinically integrated prehabilitation for people with cancer. Importantly, to maximize generalizability to clinical care, as well a sustainable model of delivery, this study uses a referral-based enrolment strategy for a broad range of oncology patients who are identified as frail or vulnerable to adverse surgical outcomes. Related to our objectives of determining the appropriateness of referrals, a key learning outcome of our research will be the estimated frailty of referred patients using the Clinical Frailty Scale (3) and how those ratings correspond with other markers of frailty and performance, as well as prehabilitation adherence and study retention.

Within the context of a pragmatic trial design, we elected to offer two streams of prehabilitation, FBP and HBP, which are selected by participants using a shared decision-making strategy with a member of the research team. Advantages to the preference-based design include better motivation and compliance with an intervention, and subsequently more favourable experiences and outcomes than they may have in their non-preferred study arm (71). Moreover, preference for a study arm can enhance external validity and generalizability to clinical practice (72–75). In clinical settings, patients' preferences, facilitators, and barriers to participation, intervention efficacy, and equitable access to services are fundamental considerations in designing and delivering health services and are core outcomes for implementation research (76–78). As such, offering both FBP and HBP options are likely to satisfy patients' needs and capacities to ensure greatest benefit to all who are referred and examination of participation across study arms will yield novel and important insight into delivery models.

The COVID-19 pandemic has created unprecedented, systemic delays in surgical procedures that are negatively affecting elective surgery patients worldwide. Evidence is rapidly mounting regarding the significant physiological and psychosocial stress due to progressive symptoms and disease status, physical inactivity, poor nutrition and economic hardship for patients awaiting surgery. These, unfortunately, are compounded with uncertainty of surgical outcomes, social isolation, fear of COVID-19 infection, and lack of access to healthcare supports that collectively will likely contribute to a substantially higher risk of surgical complications, longer and poorer recovery, and greater health system cost. Strategies to mitigate rapidly declining preoperative health are needed, especially to manage the eventual surge in surgical demand as postponed procedures are resumed or become urgently required. Prehabilitation represents an important strategy to combat the pandemic-related patient and health system challenges of surgical delays given its capacity to adapt to a contactless model of care as well as providing ongoing support to those with distance-related barriers or apprehension about visiting facilities (79, 80).

There are several strengths of this study. First, the pragmatic, preference-based trial design with robust implementation feasibility outcomes and measures of effectiveness will add important information to the prehabilitation literature that is currently lacking in these areas. Second, the prehabilitation interventions are multimodal and comprehensive within each modality intended to replicate gold-standard practice. Moreover, the interventionists represent the appropriate scopes of practice and clinical professions most qualified and likely to be involved in an interprofessional, multimodal clinical prehabilitation service. Third, by including a usual care arm, we have a control comparator for effect size estimates. Fourth, we have amended our research protocol to respond to the evolving context of the COVID-19 pandemic by pivoting towards contactless study participation. This study also has noteworthy limitations. The sample size will likely lack the statistical power to draw precise conclusions about the effect of the interventions. Similarly, in the absence of an RCT design, our interpretations of comparisons with usual care participants may be limited due to group differences in those who do versus those who do not wish to engage in prehabilitation. Interpretation of the findings will also be limited to the types of surgeries for which prehabilitation precedes which may be skewed to the physicians and healthcare teams who are in favour of prehabilitation and refer patients to

BOX 2. COVID-19 Pandemic-Related Study Accommodations.

1. Extension of enrolment period by at least 6 months to accommodate pauses in research and to initiate contactless study protocols
2. Accept form-fillable PDF referrals by email from clinicians (*versus* referrals by fax)
3. Informed consent is obtained verbally, by phone, with informed consent documentation emailed to participants to be completed and returned at their next hospital visit (*e.g.*, date of surgery, post-operative clinic visit)
4. All interactions between participants and study staff, including the baseline assessment, are completed by telephone or web conferencing (Microsoft Teams, Redmond, Washington, USA)
5. Exercise equipment, manuals, and protein supplementation are mailed to participants
6. All exercise sessions are intended to be conducted at-home and employ the same exercise parameters for HBP described in **Table 1**. Additional emphasis on strategies to maintain social distancing is provided for those who are engaging in outdoor exercise.
7. Study outcomes requiring an in-person assessment (*e.g.*, 6MWT, body composition, grip strength) are omitted during in-person research restrictions, and only data derived from questionnaires and the electronic medical record are collected for exploratory analyses of effectiveness

our study. This highlights potential sampling and participation biases as participants will more likely be referred and participate in our program if their healthcare team implicitly endorses it by virtue of discussing it and making a referral. Similarly, the breadth of cancer surgeries and their extreme heterogeneity within a relatively small sample will limit sub-group analyses related to estimates of intervention effect.

CONCLUSION

Prehabilitation has become an intriguing health intervention for people undergoing cancer surgery with growing evidence of its efficacy, especially in frail and at-risk populations. Despite growing interest in implementation, few studies have evaluated the feasibility of implementation and characteristics of models of care that resemble an integrated clinical service. The present study will contribute important implementation evidence regarding surgical prehabilitation programming while providing estimates of effect for two intervention models in frail and at-risk people with cancer.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University Health Network. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Efficacy of Prehabilitation Including Exercise on Postoperative Outcomes Following Abdominal Cancer Surgery: A Systematic Review and Meta-Analysis

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Objectives: This systematic review set out to identify, evaluate and synthesise the evidence examining the effect of prehabilitation including exercise on postoperative outcomes following abdominal cancer surgery.

Methods: Five electronic databases (MEDLINE 1946-2020, EMBASE 1947-2020, CINAHL 1937-2020, PEDro 1999-2020, and Cochrane Central Registry of Controlled Trials 1991-2020) were systematically searched (until August 2020) for randomised controlled trials (RCTs) that investigated the effects of prehabilitation interventions in patients undergoing abdominal cancer surgery. This review included any form of prehabilitation either unimodal or multimodal that included whole body and/or respiratory exercises as a stand-alone intervention or in addition to other prehabilitation interventions (such as nutrition and psychology) compared to standard care.

Results: Twenty-two studies were included in the systematic review and 21 studies in the meta-analysis. There was moderate quality of evidence that multimodal prehabilitation improves pre-operative functional capacity as measured by 6 min walk distance (Mean difference [MD] 33.09 metres, 95% CI 17.69–48.50; $p = <0.01$) but improvement in cardiorespiratory fitness such as preoperative oxygen consumption at peak exercise (VO_2 peak; MD 1.74 mL/kg/min, 95% CI −0.03–3.50; $p = 0.05$) and anaerobic threshold (AT; MD 1.21 mL/kg/min, 95% CI −0.34–2.76; $p = 0.13$) were not significant. A reduction in hospital length of stay (MD 3.68 days, 95% CI 0.92–6.44; $p = 0.009$) was observed but no effect was observed for postoperative complications (Odds Ratio [OR] 0.81, 95% CI 0.55–1.18; $p = 0.27$), pulmonary complications (OR 0.53, 95% CI 0.28–1.01; $p = 0.05$), hospital re-admission (OR 1.07, 95% CI 0.61–1.90; $p = 0.81$) or postoperative mortality (OR 0.95, 95% CI 0.43–2.09, $p = 0.90$).

Conclusion: Multimodal prehabilitation improves preoperative functional capacity with reduction in hospital length of stay. This supports the need for ongoing

research on innovative cost-effective prehabilitation approaches, research within large multicentre studies to verify this effect and to explore implementation strategies within clinical practise.

Keywords: prehabilitation, cancer, systematic review, surgery, meta-analysis

INTRODUCTION

Healthcare is under increasing pressure to ensure that perioperative care is patient-centred and value-based (1–4). "Prehabilitation" aims to optimise physiological reserve and address modifiable risk factors prior to surgery to improve postoperative outcomes (2). In cancer care, prehabilitation is a process on the continuum of care that occurs between cancer diagnosis and the beginning of acute treatment (usually surgery) (5) and includes interventions that promote physical and psychological health to reduce the incidence and/or severity of future impairments. Previously, prehabilitation programs focused solely on unimodal exercise interventions however recently there has been a growing evidence-base supporting multimodal prehabilitation including respiratory, aerobic and/or resistance training programs as well as nutritional and psychological interventions (6).

There are conflicting results regarding the effectiveness of prehabilitation in patients with cancer awaiting surgery (7, 8). Similarly, the optimal approach to delivering prehabilitation is unknown with programs differing in terms of exercise type, training frequency, intensity, duration and supervision, and thus therapeutic validity (7). While multimodal programs may intuitively be the best way to support patients with cancer there is limited evidence supporting superiority of multimodal vs. unimodal interventions (6).

Although individual programs have been shown to increase preoperative fitness (9), heterogeneity in study designs has limited the synthesis of evidence regarding effects on postoperative outcomes in those undergoing abdominal surgery for cancer (6, 7). Several randomised controlled trials (RCTs) (8, 10–15) have been published since the last systematic review in this field of research (7). This systematic review set out to evaluate and synthesise the evidence examining the effect of prehabilitation on postoperative outcomes in patients undergoing abdominal cancer surgery.

METHODS

This systematic review was conducted in accordance with the Cochrane Collaboration methods (16), reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist (17) and registered with the International Prospective Register of Systematic Reviews (PROSPERO 2020 CRD42020166551).

Study Selection

RCTs and pseudo-randomised controlled trials (such as those that allocate participants to groups based on location of residence or date of assessment) of prehabilitation, including whole body or respiratory exercise, for adults (18 years) preparing for major abdominal cancer surgery that were published in English between January 2010 and August 2020 and met the inclusion criteria (**Table 1**) were identified by using our predefined search criteria (**Supplementary Material 1**) within the following databases: Ovid MEDLINE, Embase Classic+Embase, CINAHL Complete, Cochrane Central Register of Controlled Trials and PEDro (Physiotherapy Evidence database). Given that prehabilitation is a rapidly evolving field of research we restricted our search to publications within the last 10 years (January 1st, 2010 onwards). Reference lists of identified studies were reviewed for additional references. An additional rerun of the search criteria was conducted in August 2020 for any recently published studies.

Search results were imported into the Covidence systematic literature review software program (https://www.covidence.org; Veritas Health Innovation Ltd, Australia) (18). Two of the review authors (JW, OM) independently screened the identified studies based on their title and abstract. When there was insufficient information to determine eligibility, full texts were retrieved and screened. A third researcher (LD, LE) was available for discussion could a consensus not be reached between the two reviewers on study inclusion.

Data Extraction

Two of the review authors (JW, OM) independently extracted data from the included studies using a standardised form. The clinical and outcome data extracted included the patient's baseline characteristics, baseline cardiorespiratory fitness, functional capacity after prehabilitation, postoperative complications, ICU usage, hospital length of stay, hospital re-admission and postoperative mortality. Data were entered into Review Manager 5.4 to examine appropriateness for meta-analysis (19).

Prehabilitation program data were also extracted. These included program timeframes, components of multimodal interventions and details of the exercise intervention according to the consensus exercise reporting template (CERT) (20). The CERT is a 16-item checklist developed by an international panel of exercise experts that contains seven categories: materials, provider, delivery, location, dosage, tailoring and compliance. The CERT (**Supplementary Material 1**) describes exercise interventions and assists with the evaluation and understanding of exercise parameters (20).

Data Synthesis and Analysis

Data were extracted from the included studies, pooled and analysed using random effects models after consideration of heterogeneity between the various studies. For continuous outcomes, data were calculated as mean differences (MD) when data were on a uniform scale and standardised mean differences

TABLE 1 | Inclusion criteria.

Criteria	Category	Description
Inclusion criteria	Design	• RCTs or pseudo RCTs
	Participants	• Adults 18 years scheduled to undergo abdominal surgery for cancer with at least 10 study participants.
	Intervention	• Studies that evaluated a modality of exercise prehabilitation, including whole body or respiratory exercises, including education as a stand-alone intervention or included with a framework of multimodal interventions
	Comparison	• A similar patient-group that was not exposed to a prehabilitation program (e.g., standard care with no intervention).
	Outcome measures	• Studies that include a measure of cardiorespiratory fitness/functional capacity and/or measures of postoperative outcome

RCTs, randomised controlled trials.

(SMD) with 95% confidence intervals (95% CI) when data were presented using different scales. The estimated effect size was calculated for outcomes reported in three or more studies. For dichotomous variables, individual and pooled statistics were calculated as odds ratios (OR) with 95% CI. The 95% prediction interval (95% PI; **Supplementary Material 1**), an index that describes the true effect size for 95% of all comparable studies was used to assess heterogeneity (21). PIs were used instead of the inconsistency index (I^2), which has been shown to over or under-estimate the true effect size across studies due to sampling error (21). PIs were calculated using an excel spreadsheet developed by Dr. Michael Borenstein, available at https://meta-analysis-books.com/. A $p < 0.05$ was considered to indicate statistical significance.

For continuous outcomes differences of means and variance of difference of means were obtained directly from the study results or calculated from the mean, variance and statistical significance on pre- and post- intervention assessments using RevMan meta-analysis software package (19) and the downloadable RevMan calculator available from Cochrane training (https://training.cochrane.org/resource/revman-calculator). Where the mean and SD of the change from baseline to endpoint were not reported in the original articles, the following equations were used to calculate them (16).

$$Mean_{change} = Mean_{endpoint} - Mean_{baseline}$$

$$SD_{change} = \sqrt{(SD_{baseline})^2 + (SD_{endpoint})^2 - 2 \times r \times SD_{baseline} \times SD_{endpoint}}$$

where r represents the correlation coefficient. We took $r = 0.4$ as a conservative estimate in this study (22).

Where data aggregation was not possible, due to clinical, methodological, or statistical heterogeneity, these results were summarised narratively.

Quality of evidence was analysed using the Grades of Research, Assessment, Development and Evaluation (GRADE) approach, which measures studies on six domains; study design grade, risk of bias, heterogeneity or inconsistency of effect, imprecision and publication bias to calculate a final grade (23). Data were independently appraised for the risk of bias of the included studies using version 2 of the Cochrane risk-of-bias tool for randomised trials (24).

RESULTS

The search strategy for RCTs published between January 2010 and August 2020 yielded a total of 5,147 studies, and 4,311 studies after the exclusion of duplicates. Of these, 4,005 studies were excluded based on screening the title and abstract, leaving 306 full-text articles that were assessed for eligibility. Of these 284 studies were excluded: 135 were conference abstracts, 74 were not RCTs or pseudo-RCTs, 61 did not meet our review criteria for interventions and/or outcomes, two studies did not have a comparative usual care group and 12 studies were published in a language other than English (**Figure 1** - PRISMA flow chart). Agreement between the two independent reviewers on title/abstracts and full text criteria was 91 and 96%, respectively, and two studies were referred to a third reviewer (LD) for final decision.

Meta-analysis was limited by methodological, clinical and statistical heterogeneity within the included studies. Additional data were requested for four of the studies (8, 26–28) with two able to provide the data requested (8, 27). Therefore, data was interpreted from a study figure (28), or calculated from other data within the study (26) for meta-analysis. For pooled data summary please see **Supplementary Table 11**.

Study Characteristics

In total, this review included 22 studies, of which 21 were RCTs and one a pseudo-RCT. The majority of the studies were conducted in Canada [five studies (8, 13, 26, 29, 30)] and the UK [five studies (14, 15, 28, 31, 32)]. Two were international multicentre RCTs, conducted in Australasia (27) and Europe (33). **Table 2** summarises the characteristics of studies included in the qualitative synthesis. A total of 1,700 participants were included in these studies, with sample sizes ranging from 21 to 296 patients and median ages ranging from 55 to 84 years of age across individual studies. Three studies included a variety of abdominal surgeries (27, 34, 35), seven studies focused on colorectal cancer (8, 12, 14, 15, 26, 29, 36), five on gastro-oesophageal cancer (11, 30, 33, 37, 38), four on urological cancer (13, 28, 31, 39), and single studies focused on pancreatic (10) and liver (40) cancers and one study on liver resection for colorectal metastatic disease (32).

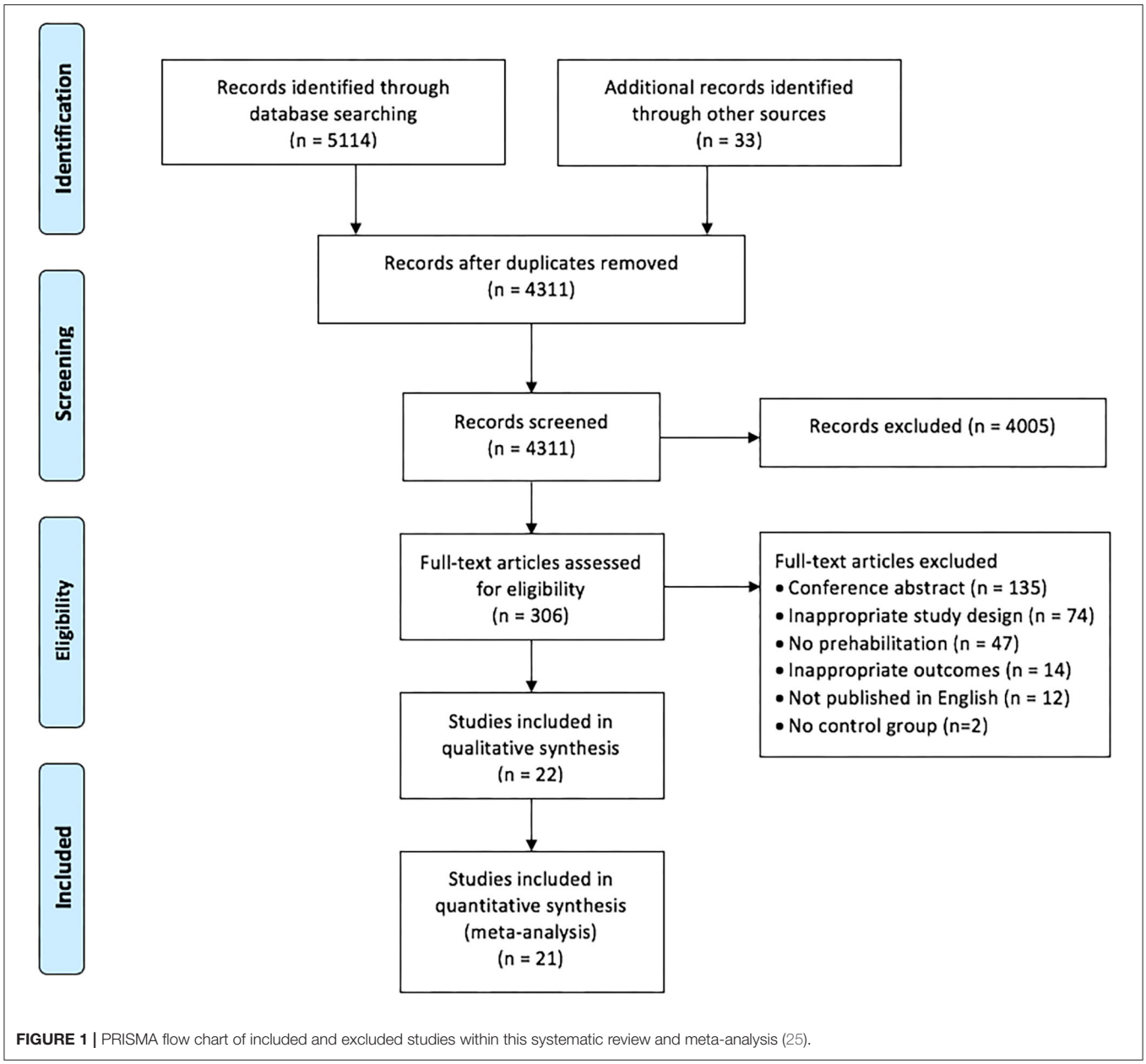

FIGURE 1 | PRISMA flow chart of included and excluded studies within this systematic review and meta-analysis (25).

Outcome Measures

Primary outcomes varied across the included studies, focusing on improving preoperative cardiorespiratory fitness (11, 28, 32), functional capacity (13, 26, 29, 30), and pulmonary function (35). Cardiorespiratory fitness was measured using Cardiopulmonary Exercise Test (CPET) variables (11, 31, 32, 34, 40) and estimated in one study using epidemiological data (36).The most common measure of functional capacity was the 6-min walk test (6MWT) (8, 12–15, 26, 29, 30, 34). Functional capacity was also measured using the 10-metre walk test (10MWT) (10), timed up and go (TUG) test (15, 36), and stair climb test (SCT) (15). Lower limb strength was measured using the 30-s sit-to-stand test (30STS) (12, 14) and chair rise time (CRT) (36).

The primary postoperative outcomes assessed included: postoperative complications (8, 10, 27, 33, 34, 38), and hospital length of stay (37, 39). Postoperative complications were measured using several different outcome measures, the Utrect Pneumonia Scoring System (38), Melbourne Group Score (27), Comprehensive Complications Index (8, 30) and the revised Uniform Pneumonia Score (33). The Clavien-Dindo rating scale was used to rate the severity of complications in the majority of included studies (8, 10–14, 26, 28–32, 34, 38, 39) (**Supplementary Table 1**). Some studies evaluated feasibility of the prehabilitation intervention (12, 14, 15, 31, 36) including the occurrence of serious adverse events that prevented surgery (11) or non-specific morbidity after surgery (40).

TABLE 2 | Description of included randomised controlled trials.

References	Country	Population/pathology	Age (yr) (mean ± SD, median (IQR))		Sample size, n (Male%)	
			Intervention	Control	Intervention	Control
Blackwell et al. (28)	UK	Urological cancer	71 ± 2	72 ± 4	19 (100)	21 (95)
Carli et al. (8)	Canada	Colorectal cancer	78 (72–82)	82 (75–84)	55 (53)	55 (42)
Swaminathan et al. (37)	India	Gastric cancer	56.03 ± 14.95	56.82 ± 11.27	29 (62)	29 (69)
Ausania et al. (10)	Spain	Pancreatic cancer	65.9 (38–81)‡		18 (50)	22 (59)
Christensen et al. (11)†	Denmark	Gastro-oesophageal cancer	63.9 ± 8.2	65.5 ± 7.3	21 (86)	29 (93)
Karlsson et al. (12)*	Sweden	Colorectal cancer	83.5 (76–85)	74.0 (73–76)	10 (40)	11 (36)
Minnella et al. (13)	Canada	Bladder cancer	69.7 ± 10.2	66.0 ± 10.2	35 (63)	35 (77)
Moug et al. (14)	UK	Rectal cancer	65.2 ± 11.4	66.5 ± 9.6	24 (75)	24 (54)
Northgraves et al. (15)*	UK	Colorectal surgery	64.1 ± 10.5	63.5 ± 12.5	10 (40)	11 (64)
Banerjee et al. (31)*	UK	Bladder cancer	71.6 ± 6.8	72.5 ± 8.4	30 (90)	30 (87)
Barberan-Garcia et al. (34)	Spain	Elective major abdominal surgery	71 ± 11	71 ± 10	62 (68)	63 (80)
Boden et al. (27)	International§	Upper abdominal cancer	64 ± 13.0	69 ± 11.9	148	148
Bousquet-Dion et al. (29)	Canada	Colorectal cancer	74 (67.5–78)	71 (54.5–74.5)	37 (81)	26 (62)
Minnella et al. (30)	Canada	Esophagogastric cancer	67.3 ± 7.4	68.0 ± 11.6	26 (69)	25 (80)
Valkenet et al. (33)	International§	Oesophageal cancer	63.7 ± 7.5	62.7 ± 8.9	120 (74)	121 (80)
Dunne et al. (32)	UK	Colorectal liver metastasis	61 (56–66)	62 (53–72)	20 (65)	17 (77)
Jensen et al. (39)	Denmark	Bladder cancer	69 (66–72)‖	71 (68–73)‖	50 (78)	57 (70)
Yamana et al. (38)	Japan	Oesophageal cancer	68.33 ± 7.64	65.90 ± 9.50	30 (80)	30 (77)
Gillis et al. (26)	Canada	Colorectal cancer	65.7 ± 13.6	66.0 ± 9.1	38 (55)	39 (69)
Kaibori et al. (40)	Japan	Hepatocellular carcinoma	68.0 ± 9.1	71.3 ± 8.8	25 (68)	26 (73)
Soares et al. (35)	Brazil	Upper abdominal cancer	58.5 (51.3–63.5)	55.0 (49.3–64.3)	16 (50)	16 (56)
Dronkers et al. (36)	Netherlands	Colon cancer patients aged >60 years	71.1 ± 6.3	68.8 ± 6.4	22 (68)	20 (80)

**Feasibility Randomised Controlled Trial.* † *Pseudo-randomised controlled trial.* ‡*median (range), group ages not reported.* §*International: Valkenet 2018: Netherlands, Belgium, Ireland and Finland, Boden 2018: Australian and New Zealand.* ‖*mean (95%CI).*

Exercise Interventions

Type

The type, frequency and intensity of the prehabilitation programs varied considerably across included studies. The majority of studies included multimodal interventions (8, 10, 12, 13, 26, 29, 30, 34–36, 38–40). Unimodal interventions included exercise interventions (11, 14, 15, 28, 31, 32), breathing exercise education (27), inspiratory muscle training (33), and incentive spirometry (37). Eight included studies combined other prehabilitation interventions with exercise: including nutrition interventions (8, 10, 13, 26, 29, 30, 39, 40), respiratory exercises (10, 35, 38), IMT (12, 35, 36) and psychological interventions (8, 13, 26, 29, 34) (**Table 3**). **Table 3** summarises the prehabilitation components and **Table 4** and **Supplementary Tables 2–8** detail the exercise interventions according to the consensus reporting template (CERT) domains (20).

Equipment

Eight (35%) of the studies used a cycle-ergometer (10, 11, 15, 28, 31, 32, 34, 38) for their exercise intervention and five (22%) used inspiratory muscle training (IMT) devices (12, 33, 35–37) to deliver breathing exercise interventions.

Exercise Program Detail

Only five studies provided criteria on when to progress exercise programs based on time in the program (14, 15, 28, 34, 35), determined by the instructor (11), using rate of perceived exertion (RPE) scales (12, 26, 29, 33, 36), percentage of maximum heart rate (31) or left to the participant to self-determine the progression (39). However, eight of these studies did not provide enough detail in the paper (8, 10, 13, 30, 32, 37, 38, 40) to enable replication. Exercise programs were described in detail to allow replication in a subset of studies (8, 12–14, 28, 31, 34), with aerobic exercise described in more detail than resistance exercises (10, 26, 29, 30, 38). Only one of the included studies provided a detailed supplementary file using pictures of exercise and equipment to allow replication (11, 15). Exercise programs were general or not reported in two studies (39, 40).

Motivational Strategies

Motivational strategies included within the exercise interventions were motivational interviewing (34), relaxation exercises (8), weekly telephone calls (8, 13, 26, 29, 30), instructional booklets (26, 29), instructional videos (33), discussion of mutual expectations and motivation (39), as well as information, motivation and encouragement provided during the session (15). One study employed behaviour change theory, providing a diary with targets and motivational material as well as engaging a support person to assist (14).

TABLE 3 | Multimodal prehabilitation component.

	Exercise			Respiratory		Nutrition	Psychology	Education session
	Aerobic	Resistance	Stretching	Exercises	IMT			
Multimodal								
Carli et al. (8)	√	√				√	√	√
Ausania et al. (10)	√	√		√		√		
Karlsson et al. (12)	√	√			√			
Minnella et al. (13)	√	√				√	√	
Barbaren-Garcia et al. (34)	√*	√					√	
Bousquet-Dion et al. (29)	√	√	√			√	√	
Minnella et al. (30)	√	√				√		
Jensen et al. (39)	√	√				√		√
Yamana et al. (38)	√	√		√				√
Gillis et al. (26)	√	√				√	√	
Kaibori et al. (40)	√		√			√		
Soares et al. (35)	√	√	√	√	√			
Dronkers et al. (36)	√	√			√			
Unimodal								
Blackwell et al. (28)	√*							
Swaminathan et al. (37)				√†				
Christensen et al. (11)	√*	√						
Moug et al. (14)	√							
Northgraves et al. (15)	√	√						
Banerjee et al. (31)	√*							
Boden et al. (27)								√
Valkenet et al. (33)					√			
Dunne et al. (32)	√*							

High-intensity interval training.† Incentive spirometry. Further details on Exercise Component can be found in* ***Table 4**. IMT, Inspiratory Muscle Training.*

Supervision/Adherence

Twelve (55%) studies included some element of supervised intervention and ranged from one session (33) followed by a home program and up to three 60 min sessions per week (32, 34, 36, 40). Attendance at supervised exercise sessions measured adherence to treatment in six studies (8, 11, 28, 29, 31, 32, 34, 36), with one study also recording interruptions to attended sessions (15). Other studies monitored adherence using self-reporting in diaries and weekly follow-up phone calls. In IMT interventions, the number of home-based sessions was measured directly using the IMT device (12).

Frequency

The frequency and duration of programs varied from five sessions over a 1 week period (10) to three times per week for 8 weeks (26) with the exception of one study which occurred concurrently with neoadjuvant treatment and lasted up to 17 weeks (14). Interval training was utilised in six studies, with five prescribing high intensity interval cycling training (11, 28, 31, 32, 34) and one study including walking intervals (12).

Qualifications of Personnel

The providers of the intervention included a range of healthcare disciplines: physiotherapists (10, 12, 27, 33, 34, 36, 38, 39), kinesiologists (8, 13, 26, 29), physician (28), exercise science staff (31), study coordinators (14), trained fitness instructors (11, 15) or a combination (40). In one study the exercise intervention was prescribed by a physician and then demonstrated and monitored by a kinesiologist (32). Qualifications of personnel supervising the intervention were not reported in three studies (32, 35, 37). Thirteen (59%) of the studies were delivered individually (one-on-one) (12–15, 26–28, 30, 33, 34, 37–39, 41), while the remaining studies did not state how they were delivered.

Setting

Programs were most commonly delivered in a home-based setting (12, 13, 26, 30, 37, 39), hospital outpatient clinics (10, 27, 36), or a combination of hospital outpatient clinic and home-based settings (8, 33). Other sites included: exercise laboratories (15, 28, 29, 31, 32), rehabilitation centres (38), hospital research unit (11), combination of home-based and community (14), community program (34) or was not specifically reported (35, 40). Individualised exercise prescriptions were common in

TABLE 4 | Description of exercise prehabilitation intervention arms according to consensus exercise reporting template (CERT) domains (20) for three of the RCTs that included multimodal prehabilitation interventions as an example.

CERT domain	Item no. and abbreviated item description	2020 Carli (8)	2018 Barberan-Garcia (34)	2018 Minnella (30)
What	1. Type of exercise equipment	Recumbent stepper Resistance bands	Cycle-ergometer stationary bicycle	Resistance bands
Who	2. Qualifications, teaching/supervising expertise and/or training of the exercise instructor	Kinesiologist	Specialised Physiotherapist	Physician prescribed; Kinesiologist demonstrated
How	3. Whether exercise are performed individually or in a group	Not specified	Individually	Individual
	4. Whether exercises are supervised or unsupervised	Supervised and home based	Supervised	Unsupervised
	5. Measurement and reporting of adherence to exercise	Attendance at the in-hospital exercise session. Self-reported in diary and weekly telephone calls	Attendance at exercise sessions	Self-reported logbook Weekly telephone calls with kinesiologist
	6. Details of motivation strategies	CD with audio instructions. Weekly telephone calls	Motivational Interviewing and objective setting prior to exercise program and revisited throughout program	Weekly telephone calls with kinesiologist
	7. Decision rules for progressing the exercise program	No details in paper—references Bousquet-Dion 2018 for reporting of intervention	Peak work rate increased by ∼5% every week up to a maximum of 85% peak work rate and 50% peak work rate for active rest.	Not reported
	8. Each exercise is described so that it can be replicated (e.g., illustrations, photographs)	No details in paper—references Bousquet-Dion 2018 for reporting of intervention	Detailed description provided	Aerobic described in terms of time, type, intensity (RPE), resistance less described
	9. Content of any home program component	Personalised progression of mod aerobic—30 min walking and resistance training x3/week	Personalised walking program focusing on increasing steps per day (using pedometer) and optimisation of walking intensity (using BORG scale)	All home based
	10. Non exercised components	Nutrition intervention +/– protein supplementation, psychology assessment, and personalised coping strategies, counselling for smoking and alcohol cessation.	Motivational interview	Nutrition assessment and supplements as needed.
	11. How adverse events that occur during exercise are documented and managed	No adverse events	No adverse events reported	No adverse events reported
Where	12. Setting in which exercises are performed	Hospital prehabilitation unit and home based	Community	Home based
When, how much	13. Detailed description of the exercises (e.g., set, reps, ration, intensity)	1 supervised session per week for 4 weeks. Warm up: 5 min Aerobic: 30 min moderate intensity Resistance: 25 min, Stretching: 5 min	1–3 sessions per week Duration: 47 min Warm up: 5 min 30% peak work rate Intervals: 2 min 70%peak work rate, 3 min active rest 40% peak work rate Cool Down: 5 min 20% peak work rate Cycling Rate: 60-70RPM	Aerobic-−3 per week of 30 min moderate continuous training (incl 5 min warm up, 5 min cool down) BORG 12–13 Strengthening 1 per week of 30 min (incl 5 min flexibility and 5 min stretching)−−3 sets x8-12 reps of 8 muscle groups.
Tailoring	14. Whether exercises are generic ("one size fits all") or tailored to the individual	Personalised	Patient specific program	Individualised
	15. Decision rule that determines the starting level of exercise	No detail in paper—references Bousquet-Dion 2018 for reporting intervention.	Cardiopulmonary Exercise Test	Based on personal level and attitude. Based on BORG or 10 point resistance intensity scale.
How well	15. Whether the exercise intervention is delivered and performed as planned	Attendance of hospital sessions—mean (SD) 68% (38). Overall adherence 80% (27)	Nil reported	Overall compliance with programme reported (63%)

CERT tables for all included studies can be found in ***Supplementary 1****.*
RPM, revolutions per minute; HR-max, maximum heart rate.

supervised exercise sessions however it was unclear in a number of cases whether the sessions were conducted individually (1:1) or as part of a group (8, 10, 11, 29, 31, 32, 35, 36, 40).

Adverse Events

Only one study (12) reported adverse events related to prehabilitation. The two events that were reported self-resolved and did not require any additional healthcare use, including musculoskeletal pain in pre-existing injuries and one episode of dizziness.

Nutritional Intervention

Nutritional interventions were included as part of multimodal prehabilitation in eight studies (8, 10, 13, 26, 29, 30, 39, 40) however reporting of the interventions varied widely in the included studies. Assessment for nutritional intervention was conducted by a registered dietitian individually in person in six studies (8, 13, 26, 29, 30, 40) and was unreported in the other studies (10, 39). Assessment focused on achieving daily dietary intake with a focus on target protein of between 1.2 and 1.5 g/kg of ideal body weight in six studies (8, 13, 26, 29, 30, 40) and involved whey protein supplement only in participants unable to achieve this with diet alone in three studies (8, 13, 29) and administered to all participants in two studies (26, 30) to ensure this target was being met. Whey protein supplements when included where recommended in the 1 h after exercise training to maximise protein synthesis (8, 13, 26, 29) or after breakfast on non-exercise training days (30).

Details of nutritional intervention in two other studies were non-specific and would not allow for replication with detail such as "liquid oral nutrition supplements and vitamin supplements" or "nutritional screening and counselling: supportive oral supplements when recommended" (10, 39, 40). Follow up of nutritional interventions was conducted by a nutritionist in four studies (8, 13, 29, 30). Only one study detailed weekly follow up phone calls by the nutritionist (30).

Psychological Intervention

Interventions aimed at reducing pre-operative anxiety (8, 13, 26, 29) as well as a motivational interview aimed at improving compliance with program elements (34) were incorporated as part of multimodal prehabilitation programs within included studies. Interventions at reducing pre-operative anxiety were delivered by a trained psychologist (26), a psychology trained nurse (8), a psychology-trained member of the research team (29) or not reported (13). The motivational interview was conducted by a specialised physiotherapist (34). All interventions were delivered as a one-off supervised session. Interventions aimed at reducing pre-operative anxiety included relaxation and imagery techniques. Participants were provided with an audio disc of exercises for home-based practise in three studies (8, 26, 29) and were encouraged to practise the techniques from daily (13) to three times per week (26, 29). However, adherence to these home based practise sessions was only incorporated into overall prehabilitation compliance by self-report in weekly phone calls in one study (26).

Education

Other educational elements included in multimodal prehabilitation programs included preoperative smoking and alcohol cessation information in three studies (8, 38, 39), however the reporting of who delivered this information, when, where and how was poor. Only one of the three studies reported that the information was delivered in person and individually by a psychology training nurse as part of the psychological intervention appointment (8).

Control Groups

Prehabilitation was compared to control groups which included standard care that included no prehabilitation intervention. Standard care varied across the included studies. Eleven studies included control groups with no intervention (11–14, 30, 32–35, 38, 39), three studies asked participants to maintain their current exercise and lifestyle habits (15, 28, 31) whereas three studies delivered the same multimodal intervention in the post-operative period instead of the preoperative period (8, 26, 29). Usual or standard care differed significantly amongst the remaining studies including physical activity recommendations (12), physical activity recommendation delivered in conjunction with nutrition counselling and advice for smoking cessation (10, 11, 36, 39) or breathing exercise information (27, 36) or was not standardised and according to local policies as in the case of a multicentre trial (33). When physical activity was recommended as part of usual care there were no limits placed on participants and participants were advised to follow clinical advice (32) and/or allowed to participate in any hospital or municipality-based exercise program (11).

Functional Outcomes and Cardiopulmonary Fitness

Five studies (28, 31, 32, 34, 36) measured cardiorespiratory fitness using oxygen consumption at peak exercise (VO_2 peak). However, only three of the studies reported VO_2 peak in comparable indices that allowed inclusion within the meta-analysis (**Figure 2**) (28, 31, 32). The meta-analysis of change in VO_2 peak from baseline to after prehabilitation in these three studies ($n = 121$ participants) demonstrated a low quality evidence of improvement in cardiopulmonary fitness but did not achieve statistical significance (MD 1.74, 95% CI −0.03–3.50 mL/kg/min; $p = 0.05$; 95% PI −9.67 to 13.15; **Figure 2**). Of the studies that could not be included in the meta-analysis, one reported significantly increased (135%; $p < 0.0001$) endurance time with cycling at a constant work-rate at 80% of peak oxygen uptake (34) while the remaining study (36), which estimated maximal aerobic capacity using epidemiological data, reported no change after the exercise prehabilitation program (29.4 ± 9.5 to 27.6 ± 6.5 mL/kg/min; $p = 0.47$). Three studies (28, 31, 32) reported oxygen consumption at anaerobic threshold (AT) and meta-analysis demonstrated low quality evidence with no significant change after prehabilitation (MD 1.21, 95% CI −0.34–2.76 mL/kg/min; $p = 0.13$; 95% PI −16.33–18.75; **Figure 3**).

Ten studies (8, 12–15, 26, 29, 30, 34, 35) reported data on functional exercise capacity using the 6MWT. Eight studies (8, 13–15, 26, 29, 30, 34) were included in the meta-analysis,

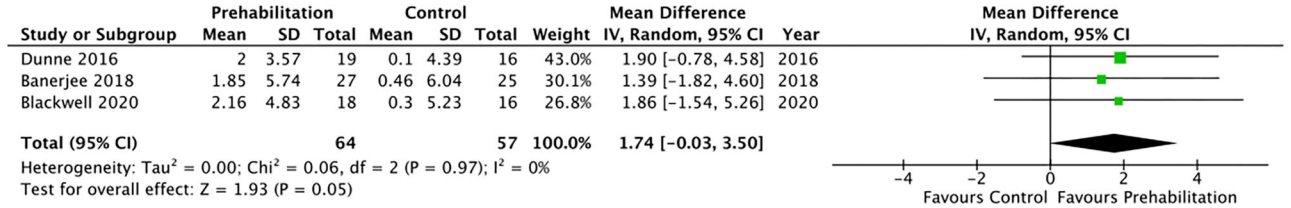

FIGURE 2 | Meta-analysis of change in oxygen consumption (VO_2) at peak (ml per kg per min) after prehabilitation.

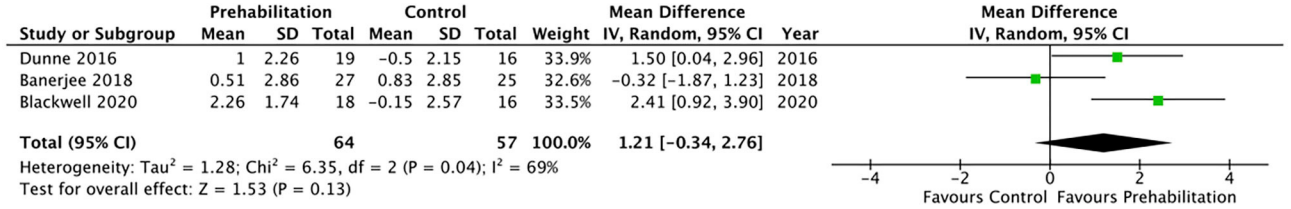

FIGURE 3 | Meta-analysis of change in anaerobic threshold (AT) (ml per kg per min) after prehabilitation.

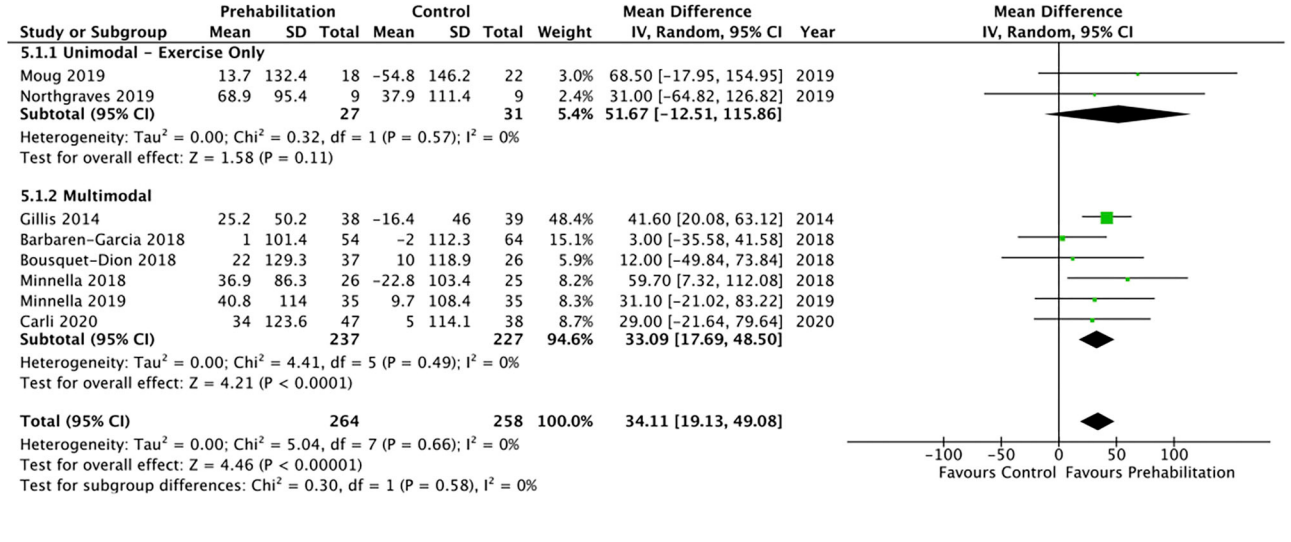

FIGURE 4 | Meta-analysis of pre-surgical change in 6MWD (m) after prehabilitation.

showing moderate quality evidence of a favourable change in 6MWT following prehabilitation with a mean difference of 34.11 metres (95% CI 19.13–49.08; $p < 0.1$; 95% PI 15.42–52.80). Subgroup analysis of multimodal interventions ($n = 6$) demonstrated a favourable change in 6MWT of 33.09 metres (95% CI 17.69–48.50; $p < 0.01$; 95% PI 11.26–54.92) whereas unimodal interventions ($n = 2$) did not achieve significance of 51.67 metres (95% CI −12.51 to 115.86; $p = 0.11$; **Figure 4**). The timed up and go (TUG) was assessed in two studies with one small study finding a pattern of improvement after prehabilitation [mean difference of −0.44 s compared to the control group 0.36 s (15)] and the other finding no significant difference after prehabilitation (7.8 s, SD ± 3.3, $p = 0.29$) (36). The stair climbing test (SCT) and five times sit to stand (FTSTS) were assessed in the same small study as the TUG, with the SCT showing a favourable improvement (mean difference of −0.32 s compared to the control group 0.12 sec) whereas no pattern of improvement was reported in the FTSTS (15). Another study showed a 19% improvement in 10 metre walk test (10MWT) in the prehabilitation group, however this was not assessed against a control group for comparison (10).

Postoperative Outcomes

Overall postoperative complications were measured in 16 studies and meta-analysis did not achieve significance (OR 0.81, 95% CI 0.55–1.18; $p = 0.27$; 95% PI 0.26–2.50; **Figure 5**). A trend

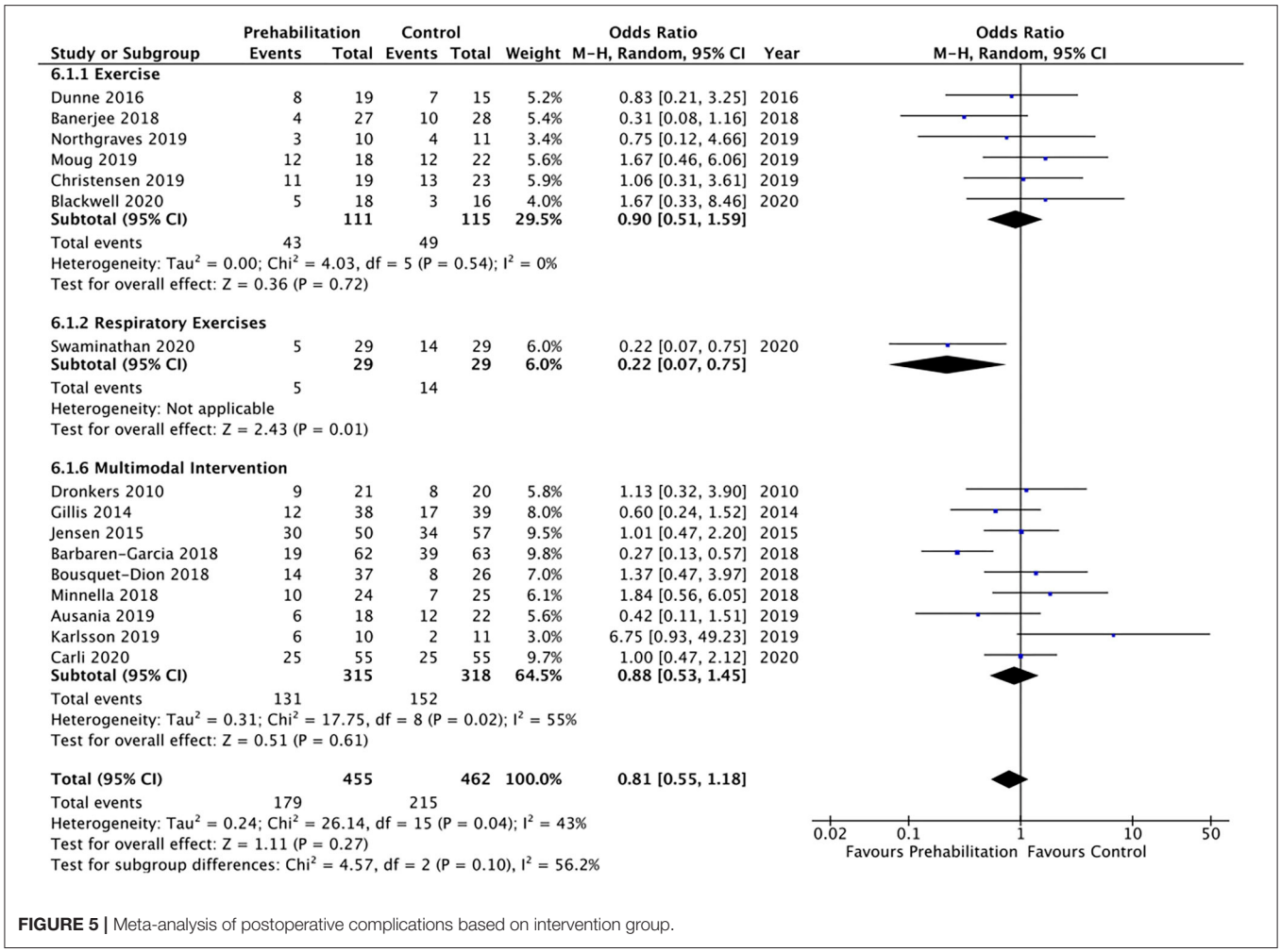

FIGURE 5 | Meta-analysis of postoperative complications based on intervention group.

was noted towards a reduction in postoperative pulmonary complications by prehabilitation, with the meta-analysis of the seven studies (26, 27, 32–36) that explored this endpoint, but this did not achieve statistical significance (OR 0.53, 95% CI 0.28–1.01; $p = 0.05$; 95% PI 0.09–3.02; **Figure 6**).

Twenty of the included studies described hospital length of stay, however only four of the included studies (33, 34, 36, 40) reported data that was able to be included in a meta-analysis. The meta-analysis demonstrated moderate quality evidence favouring prehabilitation with a mean reduction of at least 3 days of hospital stay (MD 3.68, 95% CI 0.92–6.44; $p = 0.009$ and 95% PI −9.74 to 2.38; **Figure 7**). The meta-analysis of six studies (8, 13, 26, 29, 30, 39) showed moderate quality evidence with no significant difference in 30-day hospital re-admissions between prehabilitation and control groups (OR 1.07, 95% CI 0.61–1.90; $p = 0.81$ and 95% PI 0.47–2.41; **Figure 8**). Similarly, for the seven studies (27, 30, 33–35, 39, 40) that evaluated data on mortality the meta-analysis showed low quality evidence for no significant difference in mortality outcomes between patients that received prehabilitation or standard care (OR 0.95, 95% CI 0.43–2.09, $p = 0.90$, 95% PI 0.34–2.67; **Figure 9**).

Risk of Bias and Quality of Evidence

Ten studies were assessed as having low risk of bias (**Figure 10**) (12–14, 27–30, 32, 33, 38). Two studies were assessed as having a high risk of bias (8, 11) due to pseudo-randomisation based on geographical locations (11) and due to the uneven adherence to programs in the intervention and control groups (8). The majority of studies were assessed as having some concern regarding the risk of bias, as although several of the studies were registered in clinical trial registries prior data analysis plans were not publicly available (13–15, 26, 28, 29, 31, 32, 34–40) however it was the authors judgement that this did not affect overall selection of reported result as this requirement has only been required for select journals in recent years. Quality of evidence evaluated using the GRADE approach are reported for meta-analyses of each outcome (**Supplementary Tables 9**, **10**).

DISCUSSION

Alongside the growing literature base (6, 7, 42) and clinical recommendations (3) prehabilitation is being increasingly adopted into clinical practise to improve postoperative outcomes (4), especially for patients with cancer (3). This systematic review

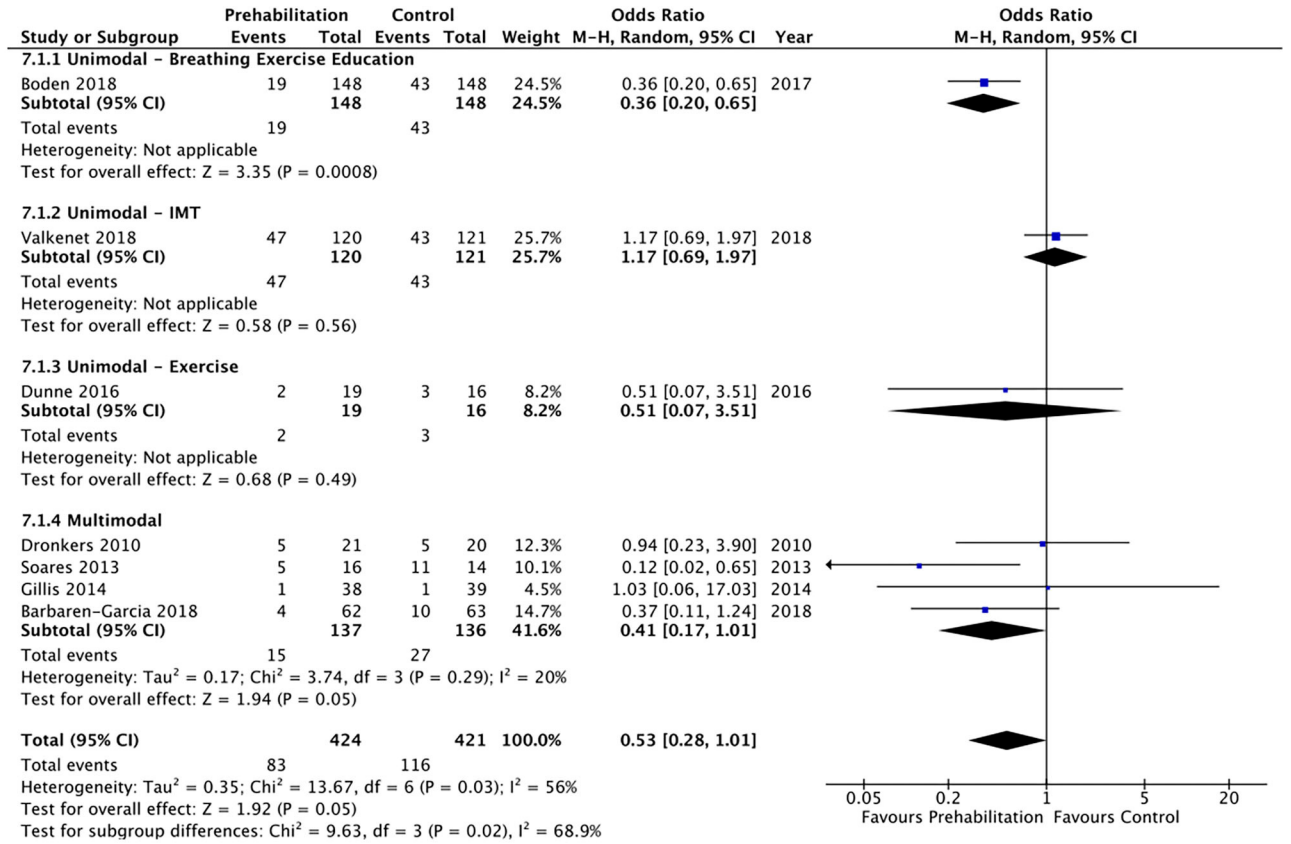

FIGURE 6 | Meta-analysis of postoperative pulmonary complications based on intervention group.

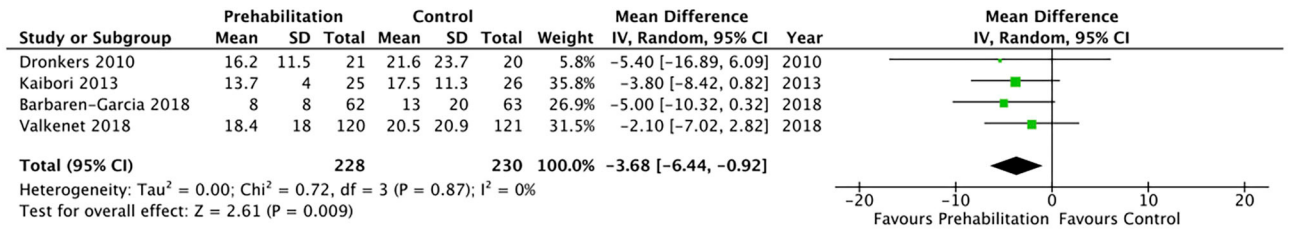

FIGURE 7 | Meta-analysis of hospital length of stay (days).

includes nine new RCTs (since the last review on this topic) (8, 10–15, 28, 37) and provides clinicians and policy makers with current research to inform future research directions and implementation strategies.

In this systematic review with meta-analysis we report that prehabilitation improves preoperative functional capacity and substantially reduces hospital length of hospital. Prehabilitation did not significantly change postoperative complications, 30-day hospital readmissions or postoperative mortality. However, these findings should be interpreted with caution, due to the substantial heterogeneity within and across the studies, small sample size of the included studies and incomplete reporting of exercise interventions. The willingness to participant must also be considered when interpreting findings as recruitment rates varied greatly within included studies and ranged from all patients approached consenting to participate (8) to as high as 65% (12) and 82% (15) of patients approached for inclusion declining to participate in prehabilitation. This acceptance may reflect individual aspects of the program suggested to influence patients waiting for cancer surgery such as delivery location, use of technology and recommendation by health professionals (43).

Improvements in surgical care, including the implementation of enhanced recovery after surgery (ERAS) pathway has

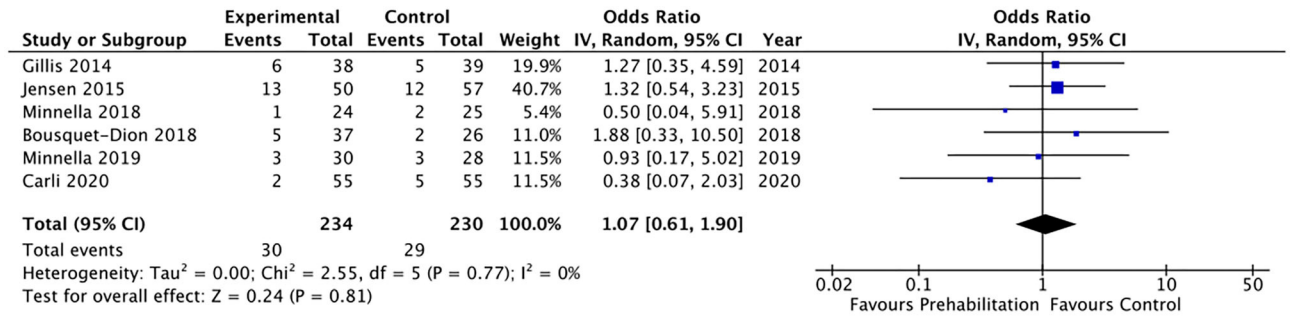

FIGURE 8 | Meta-analysis of hospital re-admission after surgery.

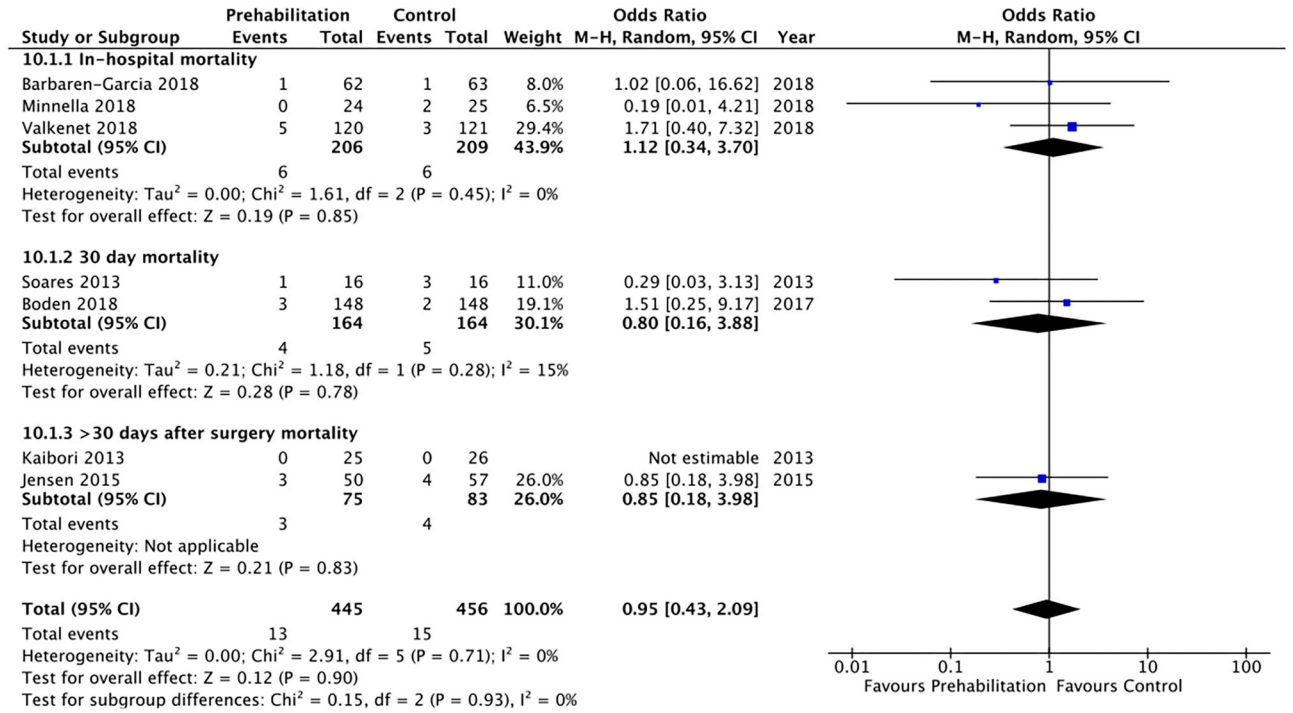

FIGURE 9 | Meta-analysis of postoperative mortality.

added complexity to interpreting the efficacy of prehabilitation interventions in the post-operative period, particularly within the inclusion of early post-operative mobilisation and pain management which are likely to influence the development of PPCs and LOS. Our meta-analysis showed a reduction in LOS, but it should be noted none of studies included a formalised ERAS pathway (33, 34, 36, 40). A recently published multicentre trial of multimodal prehabilitation program found no reduction in postoperative outcomes including LOS in frail patients awaiting colorectal resection across two centres with already established ERAS pathways (8). However, research into prehabilitation in the frail cancer population is limited (8). Therefore, it remains unclear as to whether prehabilitation offers additional benefits when established ERAS pathways are already in place or whether prehabilitation needs to be more tailored (for example provided for a longer period) within the frail population to confer these added benefits. More research is needed to investigate the efficacy of prehabilitation on post-operative outcomes in centres with already established ERAS pathways.

Our meta-analysis demonstrates that multimodal prehabilitation including exercise (combined aerobic and resistance training), nutritional intervention and anxiety reduction strategies, but not unimodal exercise, prehabilitation interventions, result in a clinically significant improvements in functional capacity as measured by 6 min walk distance (6MWD) (44). This differs from a recent systematic review conducted

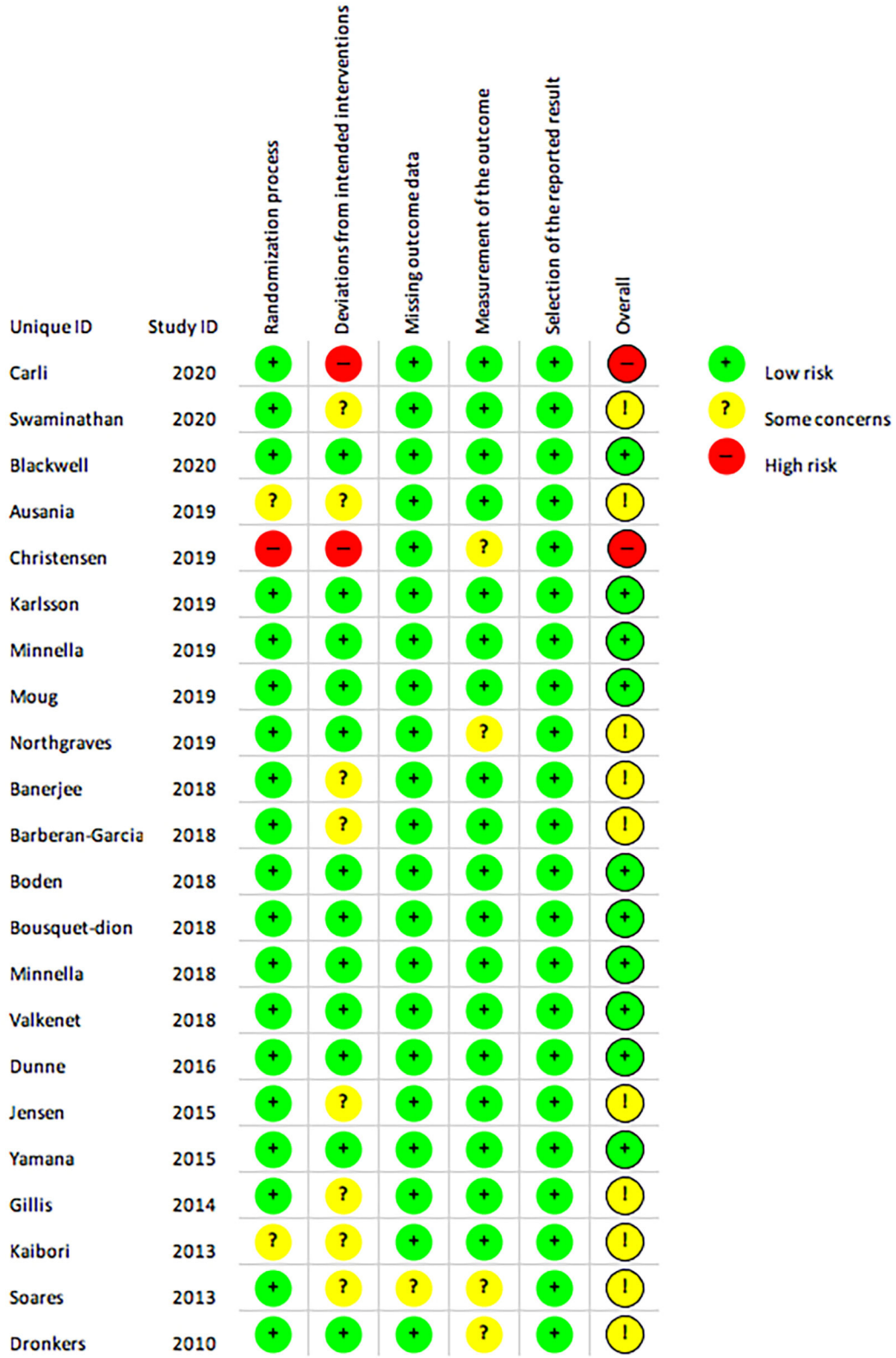

FIGURE 10 | The Cochrane risk of bias assessment of randomised controlled trials. Green (+) = low risk; Yellow (?) = unclear risk; Red (-) = high risk.

by Hughes et al. (45) who reported no significant change in pre-operative 6MWD, however this was only conducted on three studies and the availability of more recently published studies likely contributed to this difference (13–15, 29, 30, 34). The mean change in 6MWD was 33 metres with confidence intervals between 18 and 49 metres. This is a clinically relevant improvement when compared with MCID of lung cancer populations (46) of between 20 and 40 metres. There is currently no specific value reported for the abdominal surgical cancer population.

We report a trend towards improved cardiopulmonary fitness but the improvement did not reach significance. This may reflect on a limited number of studies included in the meta-analysis and underpowering of the included studies for these CPET-derived endpoints. There is a need to reflect on the heterogeneity of exercise interventions and compliance to achieve effective prehabilitation and underlying disease state that precludes some patients from responding to prehabilitation. The use of reporting templates for exercise interventions such as the CERT (20) would assist in more detailed information that could be pooled for meta-analysis as well as replication in research and implementation into clinical care (47). Huang et al. (48) reported that in those patients who were referred to a prehabilitation program there were a number of non-responders to prehabilitation. This warrants further investigation, exploring ways to improve the effectiveness of prehabilitation programs but also the importance of understanding the impact of the underlying disease state e.g., cancer associated inflammation and its associated therapies e.g., neoadjuvant chemoradiotherapy to identify responders.

There remains ongoing debate regarding the most suitable CPET variables for surgical risk prediction and for monitoring effective prehabilitation (49). A recent systematic review advocates that high-intensity (75–80% of max) constant work rate may provide increased sensitivity to changes in fitness as a result of prehabilitation (50). More importantly, is what type of exercise should be utilised within the more superior multimodal prehabilitation programs to be effective within the short timeframe that is available prior to surgery. A recent study found similar improvements in preoperative functional capacity using high-intensity interval training (HIIT) compared to moderate intensity continuous training (MICT), however at 2 months after surgery the HIIT group sustained greater physical fitness. The role of multimodal prehabilitation, that includes exercise, psychological and nutritional input is supported by this meta-analysis.

In contrast to recent reviews (45, 51) no difference was found in all-cause postoperative complications or postoperative pulmonary complications. Individual studies showed mixed results with pre-operative respiratory education (27) and multimodal interventions including exercise, IMT and respiratory exercises (35) eliciting significant reductions in postoperative pulmonary complications, whereas IMT alone was not significant (33). However, there is a lack of consistency regarding outcome measures used and timing of their application to measure the impact on postoperative complications. This prevented synthesis of findings from a greater number of studies included in the review. Abbott et al. (41) published a consensus on standardising these endpoints for pulmonary complications to enhance perioperative research, including a new definition of postoperative pulmonary complication which incorporates a measure of severity. Although many of the studies included in this meta-analysis were already in progress prior to its publication. It is promising to note that time and effort is being directed towards the standardisation of outcome measures in perioperative care research (52). However, the development of a core (minimum) set of outcome measures by multidisciplinary healthcare professionals, researchers and consumers with experience in prehabilitation will be essential to strengthen this literature base going forward.

Multimodal prehabilitation programs are increasingly implemented into standard care (4) and a multimodal approach is advised based upon results of this review (2, 3, 53). There are several large RCTs, aiming to recruit between 154 and 1,560 participants, currently in progress that will continue to strengthen this literature base (54–57). These studies include an international multicentre multimodal prehabilitation intervention including exercise, nutrition and psychological coping strategies within an ERAS protocol (Trial ID NTR5947) (55) as well as an in depth look at preoperative exercise setting by comparing hospital based supervised exercise, supported home based exercise vs. usual care in a 3-arm RCT (Trial ID ISRCTN82233115) (56), an investigation of the effectiveness of a community based prehabilitation intervention including a structured responsive exercise training program with or without psychological support (Trial ID NCT03509428) (57) as well as investigating the effectiveness of preoperative IMT (Trial ID ISRCTN10644366) (58). However, there seems to remain a blanket approach to prehabilitation despite the fact that certain groups may benefit more greatly (59) or have increasing needs (8). It may be that a stepped care model of prehabilitation (3), may be more cost effective where higher risk patients receive targeted and intensive individualised interventions and low risk patients receive more generalised universal interventions such as preoperative education, such as the approach used by Moore et al. in the implementation of a "Prehab4Cancer" program (4).

Future Directions

Much of the prehabilitation literature focuses on the immediate postoperative course of patients with certain studies focusing on functional recovery up until 8 weeks postoperatively (13, 26, 30, 60). However, there is a lack of research into how this affects return to intended oncologic (adjuvant) therapies and ongoing exercise behaviour. These offer exciting avenues of research in the future. Future research should also investigate which aspects of prehabilitation may be more effective, type and intensity of exercise, delivery settings, impact on higher risk subgroups such as the frail or elderly, impacts of biological outcomes such as inflammatory markers, the additional use of newer technologies, the cost effectiveness of prehabilitation as well as the ability to ensure patients are fit enough to withstand treatment, discharge from hospital and return as soon as possible to intended oncologic therapies. Furthermore, standardisation of outcome measures is needed to allow researchers to inform meta-analyses more effectively. This minimises research waste

and allows analysis of larger sample sizes (61, 62). Results from future studies will in turn provide guidance for clinicians and health services who provide prehabilitation and expediate implementation of prehabilitation into practise and policy.

This review benefits from robust methods in keeping with established guidelines (25), including a registered protocol. Searches were comprehensive and screening, data extraction and quality appraisal conducted in duplicate as well as exercise interventions reported according to clinical consensus guidelines (20). However, potential limitations associated with our systematic review methodology may be the restriction to studies published after Jan 1st, 2010 and the exclusion of unimodal non-exercise interventions. However, the rapidly growing area of prehabilitation warranted a focus on the most up to date literature within the context of current surgical practises. Studies were also restricted to English; however, no articles were excluded at title and abstract screening stage that appeared potentially relevant to this language restriction. The principal limitations of the findings of this study are the heterogeneity of the types of interventions and the outcome measures used to assess the effects of prehabilitation. There was also an inability to retrieve data, in response to author request, and data had to be calculated or inferred from study figures for inclusion in the meta-analysis.

In conclusion, this systematic review demonstrated that prehabilitation improved preoperative functional exercise capacity after multimodal prehabilitation programs with a reduction in hospital length of stay. These findings should however be interpreted with caution, given the heterogeneity of included studies. Never-the-less, these promising results warrant larger efficacy studies and cost-effectiveness studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

Concept, idea and research design were conducted by JW, LD, BR, and CG. Writing by JW, LD, LE, CG, and BR. Data collection by JW, OM, and LE. Data analysis by JW. Data interpretation by JW, LD, HI, LE, and BR. All authors contributed to the critical review of the manuscript before submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.628848/full#supplementary-material

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Current Landscape of Nutrition Within Prehabilitation Oncology Research: A Scoping Review

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Background: Prehabilitation aims to improve functional capacity prior to cancer treatment to achieve better psychosocial and clinical outcomes. Prehabilitation interventions vary considerably in design and delivery. In order to identify gaps in knowledge and facilitate the design of future studies, we undertook a scoping review of prehabilitation studies to map the range of work on prehabilitation being carried out in any cancer type and with a particular focus on diet or nutrition interventions.

Objectives: Firstly, to describe the type of prehabilitation programs currently being conducted. Secondly, to describe the extent to which prehabilitation studies involved aspects of nutrition, including assessment, interventions, implementation, and outcomes.

Eligibility Criteria: Any study of quantitative or qualitative design that employed a formal prehabilitation program before cancer treatment ("prehabilitation" listed in keywords, title, or abstract).

Sources of Evidence: Search was conducted in July 2020 using MEDLINE, PubMed, EMBASE, EMCARE, CINAHL, and AMED.

Charting Methods: Quantitative data were reported as frequencies. Qualitative nutrition data were charted using a framework analysis that reflects the Nutrition Care Process Model: assessment, intervention, and monitoring/evaluation of the nutrition intervention.

Results: Five hundred fifty unique articles were identified: 110 studies met inclusion criteria of a formal prehabilitation study in oncology. prehabilitation studies were mostly cohort studies (41%) or randomized-controlled trials (38%) of multimodal (49%), or

exercise-only (44%) interventions that were applied before surgery (94%). Nutrition assessment was inconsistently applied across these studies, and often conducted without validated tools (46%). Of the 110 studies, 37 (34%) included a nutrition treatment component. Half of these studies provided the goal for the nutrition component of their prehabilitation program; of these goals, less than half referenced accepted nutrition guidelines in surgery or oncology. Nutrition interventions largely consisted of counseling with dietary supplementation. The nutrition intervention was indiscernible in 24% of studies. Two-thirds of studies did not monitor the nutrition intervention nor evaluate nutrition outcomes.

Conclusion: Prehabilitation literature lacks standardized and validated nutritional assessment, is frequently conducted without evidence-based nutrition interventions, and is typically implemented without monitoring the nutrition intervention or evaluating the intervention's contribution to outcomes. We suggest that the development of a core outcome set could improve the quality of the studies, enable pooling of evidence, and address some of the research gaps identified.

Keywords: surgical nutrition, oncological nutrition, pre-operative, pre-surgery, prehabilitation

BACKGROUND

Prehabilitation interventions can be applied prior to oncological treatments, including surgery, to fortify functional reserve and enhance functional capacity to prepare patients to weather the imminent physiological and psychological stresses of treatment (1). Preoperative functional capacity is predictive of postsurgical outcomes, such as morbidity in colorectal surgery (2, 3). As an example, frail patients who cannot attain a 400-m 6-min walking distance before surgery suffer three times as many postsurgical complications as those who can walk this distance (2). In the same way, there is an extensive body of evidence that those who are undernourished, as marked by a history of weight loss and symptoms indicative of poor nutritional state, have greater surgical morbidity and mortality (4). Several prospective studies have identified that unimodal (e.g., exercise-only interventions) and multimodal (e.g., exercise interventions with nutrition optimization and/or psychological intervention) prehabilitation programs can be carried out successfully in the period before surgery to improve preoperative functional capacity (5–8).

The findings of available systematic reviews of prehabilitation, however, are somewhat inconsistent regarding effectiveness of the intervention on clinical outcomes such as postoperative complications (9, 10). These seeming contradictions are in part related to the heterogeneity of study populations, study designs, and study interventions that often cannot be melded together into one message for prehabilitation (11). Undernutrition, for instance, leads to adaptive mechanisms that tend to reduce energy expenditure in part by reducing physical activity and basal metabolism with conservation of reserves (12). As a result, malnourished patients participating in exercise-only prehabilitation might not be able to engage with or adapt to exercise and improve their functional capacity prior to surgery as well as those who are better nourished (2). The inconsistent findings of these reviews may also be attributed to the scarcity of process measures/implementation outcomes reported in the prehabilitation literature. Synthesizing and reporting data on the effectiveness of an intervention *only* limits conclusions: success or failure of any intervention is a combination of treatment effectiveness (in terms of both improved functional endpoints, and the impact on clinical outcomes, e.g., reduced postoperative complications) together with its implementation factors (13). Few, if any, reviews of prehabilitation have reported implementation factors that might influence the effectiveness of the program.

While systematic reviews summarize and assess the quality of the collective evidence of a given topic, scoping reviews determine the coverage of a body of literature on a specific topic to identify the available evidence, to examine how research in the field was conducted, and to identify and assess knowledge gaps (14). We conducted a scoping review to determine *what* and *how* interventions have been incorporated as part of prehabilitation in the oncology setting. That is, we sought to identify the type of interventions currently being conducted within prehabilitation programs, the patient populations being studied, and the study designs that have been used in research specifically labeled as "prehabilitation" (i.e., "what"). Additionally, given the relationship between nutrition and functional capacity, we sought to determine the extent to which prehabilitation studies involved nutrition, including assessment, interventions, implementation, and outcomes (i.e., "how"). We aimed to identify any research limitations or omissions that could usefully inform future research design, conduct and interpretation, or that could help improve the coherence and delivery of the nutritional aspects of prehabilitation in clinical practice.

METHODS

We performed a scoping review of the literature based on the framework outlined by Arksey and O'Malley (15),

recommendations of Levac et al. (16), and in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR). The review included the following five key phases: (1) identifying the research question, (2) identifying relevant studies, (3) study selection, (4) charting the data, and (5) collating, summarizing, and reporting the results. A project team consisting of health researchers, physicians, dietitians, an epidemiologist, and perioperative clinic managers was established to develop the research question and oversee the study.

Identifying the Research Question

The overarching goal of this scoping review was to provide an overview of current prehabilitation practices in oncology, to identify the extent to which prehabilitation programs included nutrition, and to generate recommendations for future studies based on identified gaps. Our research questions were as follows:

1. What are the study, patient, and intervention characteristics of published prehabilitation studies?
2. How many prehabilitation studies were conducted with a nutrition treatment component?
3. What are the specific (i) nutrition assessments, (ii) interventions, (iii) process measures (monitoring and evaluation), and (iv) nutrition outcomes associated with the prehabilitation studies that included a nutrition treatment component?

Identifying Relevant Studies

Given that our goal was to map current research practices in oncology-related prehabilitation, we focused our scoping review to studies of interventions applied prior to oncology treatment that were identified as either unimodal or multimodal prehabilitation; that is, published work, including protocols, that contained the term "prehabilitation" in the title, abstract, or keywords. We did not set a time limit to the search to ensure as much evidence as possible was captured.

We used broad search terms that encompassed prehab* or pre-hab* or pre-rehab* AND cancer* or oncolog* or malignan*. The final search was conducted in July 2020 using MEDLINE, PubMed, EMBASE, EMCARE, CINAHL, and AMED. Hand searching the reference lists of key papers, including all identified systematic reviews and meta-analyses of prehabilitation, were also conducted.

Study Selection

Two reviewers (CG and SD) independently reviewed titles and abstracts for inclusion. Articles were considered for full-text review if inclusion criteria were met: (1) a quantitative or qualitative study of a "prehabilitation" program; and (2) included adult patients (age >18 years) with cancer (or where the majority of participants reported in the study had cancer), treated with surgery or other oncological therapies. Studies were excluded if they were narrative reviews, editorials, commentaries, conference abstracts, or were published in a language other than English or French. Selected articles for full-text review were then independently reviewed by the two reviewers. Disagreements were addressed by discussion and consensus.

Charting the Data

The data extraction template (Microsoft 2010, Redmond, WA) was developed in consultation with the project team and included study design, cancer type, specification of the prehabilitation program, primary outcome measure, and whether nutrition was part of the formal prehabilitation program by including the use of nutritional screening/assessment or nutrition treatment. Of the studies identified as having a nutrition intervention component, quantitative and qualitative data were collected on: (1) method of nutritional assessment, (2) validated nutrition screening or assessment tool, (3) goal of the nutrition intervention including the reference standard or accepted nutritional guideline, (4) characteristics of the nutrition intervention, (5) evaluation and monitoring of the intervention, and (6) nutrition outcomes. Two researchers (CG and SD) independently extracted data for the first 10 studies to refine the data form and ensure consistent data extraction that adequately reflected the research question.

Collating and Summarizing Results

Quantitative data were analyzed using descriptive statistics (frequencies). Qualitative data were charted using a framework analysis that reflects the Nutrition Care Process Model: assessment, intervention, and monitoring/evaluation of the nutrition intervention (17). The study team were consulted in the interpretation of the findings, identifying research gaps and creating suggestions for future research.

RESULTS

Search Results

Our search identified 550 unique articles (**Figure 1**). After abstract screening, 121 articles were suitable for full-text review. Hand searching did not produce any further unique articles. Eleven articles were subsequently excluded because of language ($n = 1$), a narrative review ($n = 3$), a conference abstract ($n = 1$), no preoperative intervention ($n = 1$), or did not pertain to a prehabilitation program ($n = 5$). One-hundred and ten studies were included in the final review, of these, 34% ($n = 37$) included a nutrition intervention component.

All Prehabilitation Studies

Table 1 describes the findings for all of the prehabilitation studies. These studies were published between 2012 and 2020. Of these 110 studies, 56% ($n = 61$) were identified as primary research studies; 57% of the prehabilitation studies arose from Europe ($n = 63$) and 21% from Canada ($n = 23$). The primary studies were largely conducted as cohort designs ($n = 25$; 41%) and randomized controlled trials (RCTs) ($n = 23$; 38%). Systematic reviews, meta-analyses, and pooled analyses comprised 23% ($n = 25$) of the prehabilitation literature. Functional ($n = 40$; 36%) and clinical ($n = 25$; 23%) measures were the most frequently reported primary outcomes.

Most of the prehabilitation literature described multimodal ($n = 54$, 49%) or exercise-only prehabilitation ($n = 48$, 44%); two studies reported interventions that were exclusively nutrition related (2%) while one study reported an intervention that was exclusively psychological (1%). We identified that surgical

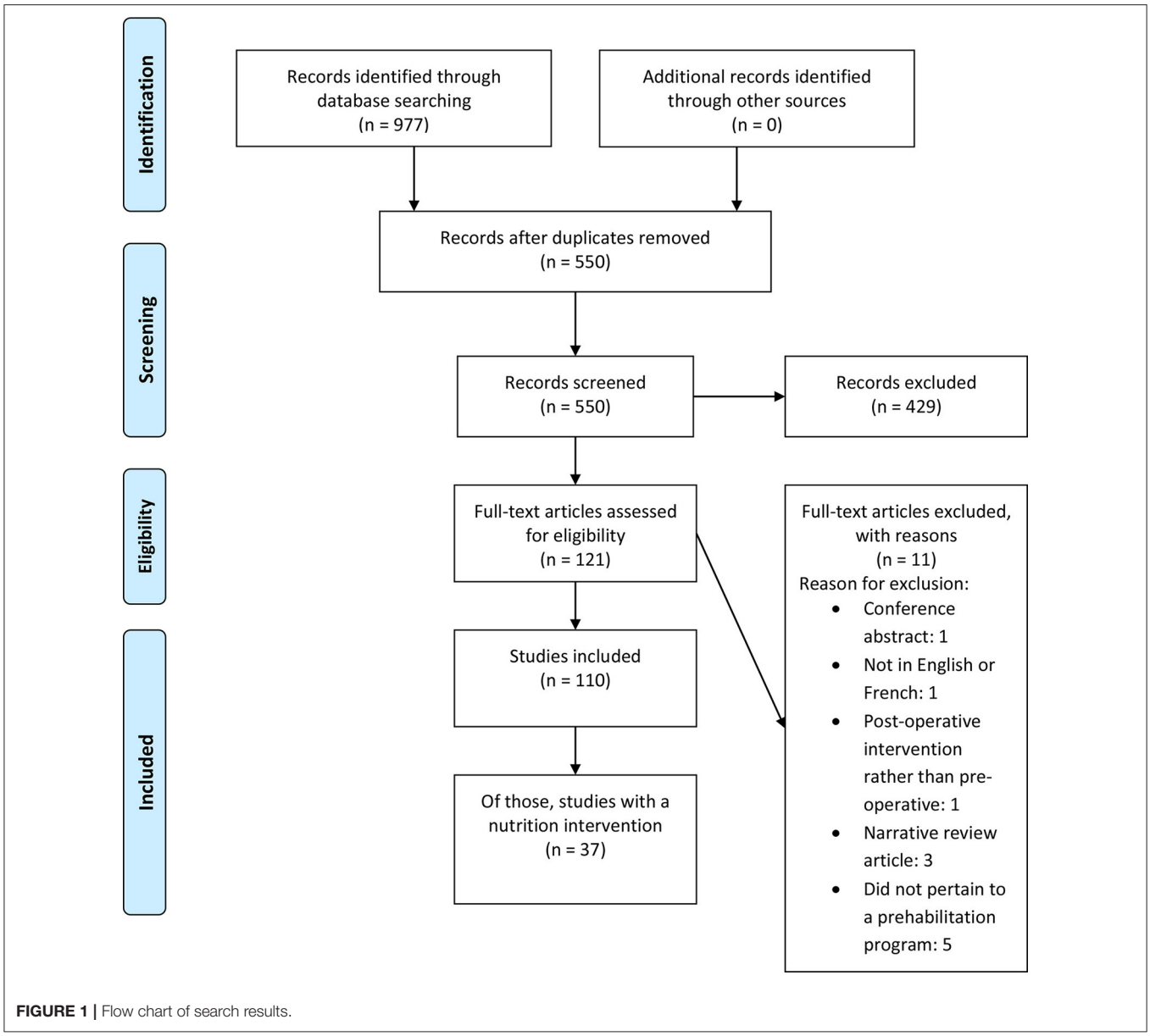

FIGURE 1 | Flow chart of search results.

prehabilitation made up 94% of the literature, with the rest related to definitive non-surgical oncological treatments. The patient populations studied most were colorectal cancer ($n = 35$; 32%) and mixed cancer types ($n = 33$; 30%).

Screening or assessment for malnutrition was conducted in one-third of prehabilitation studies ($n = 33$); approximately half of these studies used a validated tool ($n = 17$) and 39% of these studies ($n = 13$) employed a registered dietitian to conduct the screening or assessment. The person who conducted the screening/assessment was not specified in 45% of these studies.

Prehabilitation Studies With a Nutrition Treatment Component

Table 2 and **Supplementary Table 1** describe the quantitative and qualitative findings of the prehabilitation studies with a nutrition treatment component. Only 37 of the 110 studies of prehabilitation had a nutrition treatment component. The study designs were as follows: 27% ($n = 10$) were protocols (18–27), 14% ($n = 5$) were pilot studies (8, 28–31), 5% ($n = 2$) were descriptions of prehabilitation programs (32, 33), 3% ($n = 1$) were case reports (34), 3% ($n = 1$) were feasibility studies (35), and 3% were qualitative studies (36). Of these 37 studies, 30% ($n = 11$) were cohort studies (37–47) and 16% ($n = 6$) were RCTs (48–53).

Nutritional Assessment Within Prehabilitation

Seventy-eight percent ($n = 29$) of the 37 identified studies included a statement regarding the conduct of nutritional assessment [$n = 8$ studies did not include a nutritional assessment statement (20, 26, 32, 36, 39, 43, 45, 47)]; however, the application of assessment was inconsistent across studies.

TABLE 1 | Patient, study, and intervention characteristics of all prehabilitation studies.

Characteristic	Number of studies ($n = 110$)	Percentage (%)
A. ALL PREHABILITATION STUDIES		
Study characteristics		
Country		
Europe	63	57.3
Canada	23	20.9
United States	15	13.6
Asia	4	3.6
Australia	5	4.6
Published studies		
Primary studies	61	55.5
Secondary analysis	8	7.3
Systematic review	16	14.5
Meta/pooled analysis	9	8.2
Protocol	13	11.8
Implementation study/description of prehabilitation implementation	3	2.7
Study design of primary studies		
Randomized controlled trial	23	37.7
Cohort study	25	40.9
Case report	4	6.6
Pilot	9	14.8
Primary outcome		
Functional	40	36.4
Clinical	25	22.7
Patient reported	9	8.2
Nutrition outcome	1	0.9
Feasibility	17	15.5
Mixed primary outcomes	3	2.7
Not applicable/ not specified	15	13.6
Indication for prehabilitation		
Surgery	103	93.6
Definitive oncological treatment	7	6.4
Patient characteristics		
Cancer type		
Colorectal	35	31.8
Lung	9	8.2
Pancreatic	4	3.6
Bladder	4	3.6
Gastric	1	0.9
Esophageal	4	3.6
Breast	4	3.6
Prostate	7	6.4
Hematological	4	3.6
Head and neck	2	1.8
Brain	1	0.9
Gynecological	1	0.9
Mixed cancer cohort	33	30.0
Not specified	1	0.9
Intervention characteristics		
Prehabilitation intervention		
Exercise only	48	43.6
Nutrition only	2	1.8
Psychology only	1	0.9
Function only	5	4.6
Multimodal	54	49.1
B. PREHABILITATION STUDIES WITH NUTRITION SCREENING OR ASSESSMENT		
Was a nutrition screen or assessment performed?		
Yes	33	30.0
No	48	43.6
Not specified	12	10.9
Not applicable*	17	15.5
Was at least one validated screening or assessment tool used?		
Yes	17	51.5
No	15	45.5
Not specified/ enough information available	1	3.0
Was the screening or assessment performed by a registered dietitian?		
Yes	13	39.4
No	5	15.2
Not specified	15	45.4

Not applicable refers to any study that did not collect primary data.

Each study used a different method for nutritional assessment, with most studies using a combination of various nutritional assessment tools, parameters, and indicators. The most commonly used tools to screen or assess for malnutrition were Subjective Global Assessment/Patient-Generated-Subjective Global Assessment (8, 27, 31, 35, 51), Nutrition Risk Screening-2002 (8, 19, 51, 52), Mini Nutritional Assessment (23, 28, 40, 41), Simplified Nutritional Appetite Questionnaire (23, 37, 41), and Malnutrition Universal Screening Tool (22, 46). The most common nutritional parameters were pre-albumin or albumin (18, 19, 23, 34, 38, 41, 46), which were reported by 19% ($n = 7$) of studies as a nutritional parameter [although, it is not considered to robustly reflect nutritional status in patients with cancer (54)], and 27% ($n = 10$) reported use of food records or recalls (8, 18, 27, 34, 35, 48–51, 53). Forty-three percent ($n = 16$) of studies included nutritional indicators, such as weight, body mass index (BMI), or body composition as an element of the assessment (18, 19, 23, 27–30, 33, 35, 38, 40, 41, 44, 46, 50, 53). Body composition analysis included computed tomography (CT) (18), bioimpedance (19), and skinfold assessments (24, 27, 35).

Eight percent ($n = 3$) of studies stated that an assessment was conducted without providing details of the method or tool used (21, 25, 42). As examples, "Complete nutritional assessment undertaken by a registered dietitian" (42) and "A nutritionist performed a medical examination running appropriate biological tests to evaluate the nutritional status" (25). Another study provided only vague details of the nutritional parameters used—"the dietitian assessed nutritional status using … and blood vitamin B [the B-vitamin assessed was not specified]" (41). In most cases, the cut-points or criteria for nutritional risk or diagnosis of a nutrition problem requiring treatment (e.g., malnutrition) were not specified. Only 16% ($n = 6$) of studies

TABLE 2 | Study and intervention characteristics of prehabilitation studies with a nutrition component.

	Number of studies ($n = 37$)	Percentage (%)
STUDY CHARACTERISTICS		
Study design of primary studies		
Randomized controlled trial	6	16.2
Cohort study	11	29.7
Case report	1	2.7
Pilot	5	13.5
Feasibility	1	2.7
Protocol	10	27.0
Implementation study/description of prehabilitation implementation	2	5.4
Qualitative study	1	2.7
Indication for prehabilitation		
Surgery	37	100.0
Definitive oncological treatment	0	0
INTERVENTION CHARACTERISTICS		
Was a nutrition screen or assessment performed?		
Yes	29	78.4
No	8	21.6
Was an explicit goal stated for the intervention?		
Yes	21	56.8
No	16	43.2
If a goal was stated, was this referenced?		
Surgery or oncology guideline	9	42.9
Expert consensus	2	9.5
Another study referenced	3	14.3
No reference provided	7	33.3
What was the nutrition intervention?		
Supplementation only	3	8.1
Counseling only	3	8.1
Counseling (generalized or personalized) in addition to supplementation	19	51.3
Leaflet	2	5.4
Ingredients provided	1	2.7
Not enough information provided	9	24.3
If supplementation was provided, what was the type of supplementation		
Protein supplements	11	50.0
Protein supplements in addition to vitamin and/or mineral supplementation	3	13.6
High energy oral nutritional supplements	1	4.6
Immunonutrition	1	4.6
Leucine	1	4.6
Not specified	5	22.7
Was the nutrition intervention monitored or evaluated?		
Yes	11	29.7
No/not specified	26	70.3
Were any nutrition-related outcomes reported?		
Yes	16	43.2
No	21	56.8

specified their diagnostic criteria rather than cut-points (22, 23, 28, 40, 44, 46).

Nutrition Interventions Within Prehabilitation

Eleven percent ($n = 4$) of studies specified that a nutrition intervention was provided to patients "in need" without defining the mechanism for identifying these patients (18, 20, 32, 47). As an example, "Usual care for all participants included review by specialist dietitians if they were struggling nutritionally (20)." Little more than half ($n = 21$) of the prehabilitation studies with a nutrition treatment component specified a goal for the nutrition intervention; of these, 67% ($n = 14$) referenced the stated goals and only 43% ($n = 9$) used a reference standard or accepted guideline, including European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines (8, 21, 25, 35, 48–51, 53). Most goals were related to meeting estimated protein needs (8, 22, 25, 27, 28, 31, 35, 37, 48, 51, 53) or meeting estimated energy and protein needs (19, 21, 23, 39, 41, 49, 50). Protein needs were estimated at 1.2–2.0 g/kg/day and energy needs were estimated using 25–30 kcal/kg/day, indirect calorimetry, Harris Benedict equation, or WHO formula. Other stated nutrition goals included optimizing nutritional status (30), protein supplementation (32), and caloric and protein supplementation (18). Fifty-one percent ($n = 19$) of the interventions applied to meet these goals included a combination of both nutrition counseling (personalized or generalized) and supplementation (8, 18, 19, 22, 23, 25, 27, 31, 34, 35, 39, 41, 42, 48–53). Eight percent ($n = 3$) of studies used counseling alone (30, 44, 45), 5% ($n = 2$) used a leaflet (26, 36), and 8% ($n = 3$) used supplementation alone (32, 38, 46). Of the studies that used a nutrition supplement, "protein supplements" or a combination of vitamin/mineral supplements with protein supplements (8, 22, 25, 27, 31, 32, 34, 35, 38, 41, 48–51, 53) were used most often. Other supplements included high-energy oral nutrition supplements (19) and immunonutrition (46). Whey protein supplements (8, 22, 27, 31, 48–51, 53) were among the most prevalent of the protein-only supplements used in prehabilitation studies. Twenty-three percent ($n = 5$) of studies reported use of a supplement but did not provide any detail on the type of supplement used (18, 23, 39, 42, 52).

Many interventions appeared to be "personalized" to meet individual patient needs (8, 18, 19, 22, 24, 25, 32, 34, 39, 53). For some of the studies, it was clear that the nutrition assessment directed the nutrition care plan, including the need for specialized nutrition support (20, 40, 46), provision of a supplement or the supplemental dose (19, 23, 41, 49–51, 53), need for weight loss/gain (8, 27, 42, 53), or provided dietary advice based on food recalls, dietary patterns, and nutrition-impact symptoms (8, 22, 30, 31, 39, 51, 53). It was unclear how the nutritional assessment influenced the treatment plan in the remaining studies. Standardized instructions revolved around consuming protein supplements or snacks post-exercise (25, 27, 31, 35, 39, 45, 48–51, 53), increasing dietary protein intake (22, 27, 28, 34, 36, 50–52) and tips on consuming balanced meals (22, 44, 48, 53). Twenty-four percent ($n = 9$) of studies did not provide enough information for us to discern the

specific nutrition intervention (20, 21, 24, 29, 33, 37, 40, 43, 47). Examples include, "aimed to incorporate nutrition support (33)," "appropriate supplementation (18)," or leaflets or seminars that "included nutrition (29, 43)."

Monitoring and Evaluation of Nutrition Impact Within Prehabilitation

Finally, a third ($n = 11$) of studies monitored adherence to the nutrition intervention (8, 19, 22, 25, 28, 30, 35, 45, 49, 52, 53). Self-reported adherence using logbooks/dairies (8, 19, 50, 52, 53) and a mobile app (22) were reported. Twenty-four percent ($n = 9$) of studies monitored adherence and provided ongoing support through telephone calls (8, 19, 24, 28, 35, 45, 49, 50, 53). However, tailoring of the nutrition intervention based on a follow-up appointment or telephone call was reported in only 8% ($n = 3$) of studies (24, 25, 50). An objective evaluation of whether the nutrition prescription was meeting patient needs preoperatively was reported in only one study where weight was measured (30). Yet, 43% ($n = 16$) of the studies reported some form of nutrition outcome, such as weight (18, 24, 29, 30, 33, 35, 38, 44, 51), food records or questionnaire (18, 21, 27, 44), nutrition screening or assessment tools (19, 27, 35), body composition (8, 18–22, 24, 29, 51), and handgrip strength (8, 20, 24, 33, 35). Although food recalls/records were stated to be used in several studies, only one study reported intake data (fiber and fat) (44). Of note, only 5% ($n = 2$) of studies examined outcomes by sex (38, 51).

DISCUSSION

We conducted a scoping review to map the formal prehabilitation literature and identify opportunities to improve future research with particular emphasis on nutritional support. Currently, much of the available prehabilitation evidence, which could be used to inform practice and policy, is in the form of cohort studies. The majority of prehabilitation studies were conducted as multimodal or exercise-only studies and were applied before surgery. Only one-third of these studies included a dietary/nutrition treatment component. Nutrition assessment was inconsistently applied across these studies. In many studies, it was unclear how the nutrition assessment was used to identify nutrition problems or influence the treatment plan. Nearly one-quarter of these studies stated a nutrition intervention was applied without describing the intervention. Approximately half of the studies reported a nutrition treatment goal; yet, of those studies that reported a goal, one-third were not referenced at all and less than half referenced accepted nutrition guidelines in surgery or oncology. Finally, approximately two-thirds of studies did not monitor the nutrition intervention or evaluate nutrition outcomes.

This review identified several important research gaps. Firstly, two-thirds of the published literature on prehabilitation did not include nutrition risk screening or malnutrition assessment. Given that nutritional status can exert a modifying effect on nutritional (55), clinical (56, 57), and functional (58) outcomes, a failure to examine treatment effects at different levels of nutritional status limits research conclusions and clinical decision making (59–61). Effect modification is considered a natural phenomenon that should be reported and described; therefore, pooling of data should only be considered when the effect of treatment is identified to be homogenous across the strata of a potential modifying variable (e.g., nutritional status) (62). Considering a single treatment effect for prehabilitation on the impact of outcomes, independent of nutritional status, could result in a finding of a null effect (if subgroups respond to treatment in opposing ways), an overestimated, or an underestimated effect of prehabilitation treatment depending on the prevalence of malnutrition in the sample. Similarly, many studies were conducted in mixed cancer types, yet the treatment effect for prehabilitation might differ based on cancer status. While small sample sizes often preclude modification analysis, a failure to investigate heterogeneous effects could be a contributing factor to the conflicting, contradictory reports of the effect of prehabilitation on outcomes.

Overall, nutritional screening and assessment across published prehabilitation studies was heterogeneous and often completed without validated tools. Informal assessments, including clinical parameters and subjective measures result in under recognition of malnutrition (63). Valid nutritional assessment is required to identify malnutrition and any other nutrition-related problems that contribute to adverse outcomes. This finding has three important implications for prehabilitation research: (1) using non-validated tools to identify malnutrition produces findings that are subject to misclassification bias; (2) using a variety of tools to identify malnourished patients limits cross-study comparisons and synthesis of findings for meta-analysis; and (3) even validated tools cannot diagnose malnutrition with 100% sensitivity and specificity, so it is unlikely that the studies employing non-validated tools identified all the nutritionally compromised patients. The latter point is particularly problematic given that the primary outcome for most prehabilitation trials was identified to be functional and/or clinical. Malnourished patients have lower functional capacity (58, 64) and a reduced capacity to gain function through exercise alone (without first correcting malnutrition, which, for malnourished patients, could be the underlying etiology for the compromised function (58, 65, 66). A failure to correctly identify malnutrition for treatment has the potential to produce misleading findings for the effect of prehabilitation.

Of the published prehabilitation studies with a nutrition treatment component, approximately two-thirds of these studies did not monitor or evaluate the nutrition intervention. According to Proctor et al. (13), when an intervention fails to deliver, it is critical that we are able to attribute failure to either the intervention itself, the factors associated with its implementation, or a combination of the two. Inferring success or failure of the prehabilitation program using only functional and clinical endpoints is problematic as it is impossible to discern where the success or failure lies (13). As an example, we identified that 41% of nutrition prehabilitation interventions supplemented protein. Yet, it is difficult to discern whether positive or negative findings can be attributed to this intervention, or to another component of the multimodal prehabilitation, given implementation was poorly documented. If we have failed to monitor whether the nutrition prescription

met patient needs (e.g., the intervention was acceptable to the patient, it was feasible to meet estimated therapeutic targets with the given intervention), assess implementation outcomes (e.g., fidelity of the intervention against protocol or patient adherence to the prescribed intervention), or evaluate nutrition outcomes (e.g., weight stabilization for malnourished patients), we cannot conclude with confidence that the intervention itself was (un)successful. Studies that do not monitor the nutrition prescription and evaluate the outcomes, do not contribute to our collective understanding of which interventions work best, how do they work, and for whom do they work best.

Finally, almost half of the published prehabilitation studies with a nutrition treatment component did not report the goal of the nutrition intervention. Several accepted standards exist to form the basis of nutrition goals in surgery (4) or oncology (67, 68) care. This finding has two major implications for prehabilitation research. First, when the goal of an intervention is unknown, critical appraisal of the study design and study's finding is difficult. Second, it is expected that evidence-based interventions that represent accepted standards are most likely to meet patient needs consistently. Treating patients without taking cognizance of and seeking to achieve these standards increases the risk of inadequate nutritional care with the associated inferior outcomes, again, potentially contributing to conflicting findings for multimodal or nutrition prehabilitation.

In order to effectively address the research gaps identified, we recommend that a core outcome set (COS) be developed and adopted for prehabilitation studies. A COS is a standardized set of outcomes to be reported by all trials within a research field (69). Additional outcomes may be reported at the discretion of the researcher, but a minimum standardized set of outcomes would be reported, permitting cross-study comparisons and enabling data synthesis for systematic reviews or meta-analyses that inform clinical practice (70). This need is illustrated by our identification that 23% of the formal prehabilitation literature constitutes systematic reviews and meta-analyses, and many of these reviews were found to be inconclusive, citing heterogeneity as the rationale. Clearly, addressing the extent of heterogeneity would enhance data synthesis and should be seen as a priority for prehabilitation research. For nutrition, the development of a COS that includes standards for nutritional assessment, a requirement to state the goal of the intervention in relation to an appropriate reference standard, along with a standard set of measurements to monitor and evaluate the intervention, could greatly advance the literature.

We would like to acknowledge a few limitations. First, we did not register this trial; although, this is not a prerequisite for scoping reviews. Second, this review was limited to prehabilitation interventions for patients with cancer. As a result, our findings should not be generalized to all prehabilitation research. Third, our search was limited to six databases and languages of English and French; these criteria may have biased our findings. Finally, we limited our review to formal prehabilitation studies (articles with the term prehabilitation in the title, abstract or keywords); this strategy may have introduced misclassification bias. That said, there is no accepted definition of prehabilitation, and our goal was to map the range of studies currently being conducted as a form of "prehabilitation." We also acknowledge the large body of evidence of nutritional-only interventions such as preoperative nutritional support that have been reported previously that would not be included using our search strategy focusing on prehabilitation.

CONCLUSION

The prehabilitation literature is lacking standardized and validated nutritional assessment, is frequently conducted without employing evidence-based nutrition interventions, and is typically conducted without monitoring the nutrition intervention or evaluating the intervention's contribution to outcomes. In order to advance our understanding of prehabilitation, the nutrition component of prehabilitation interventions should be based on validated tools of assessment, accepted standards, monitored, and evaluated. We suggest that the development, adoption, and application of a core outcome set would be a first step in addressing the research gaps identified and result in studies that are more likely to inform clinical practice and improve patient outcomes.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

CG, SD, and MW designed the research. CG and SD carried out the data collection. All authors edited, read, and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2021.644723/full#supplementary-material

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Digital Support to Multimodal Community-Based Prehabilitation: Looking for Optimization of Health Value Generation

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Prehabilitation has shown its potential for most intra-cavity surgery patients on enhancing preoperative functional capacity and postoperative outcomes. However, its large-scale implementation is limited by several constrictions, such as: i) unsolved practicalities of the service workflow, ii) challenges associated to change management in collaborative care; iii) insufficient access to prehabilitation; iv) relevant percentage of program drop-outs; v) need for program personalization; and, vi) economical sustainability. Transferability of prehabilitation programs from the hospital setting to the community would potentially provide a new scenario with greater accessibility, as well as offer an opportunity to effectively address the aforementioned issues and, thus, optimize healthcare value generation. A core aspect to take into account for an optimal management of prehabilitation programs is to use proper technological tools enabling: i) customizable and interoperable integrated care pathways facilitating personalization of the service and effective engagement among stakeholders; ii) remote monitoring (i.e. physical activity, physiological signs and patient-reported outcomes and experience measures) to support patient adherence to the program and empowerment for self-management; and, iii) use of health risk assessment supporting decision making for personalized service selection. The current manuscript details a proposal to bring digital innovation to community-based prehabilitation programs. Moreover, this approach has the potential to be adopted by programs supporting long-term management of cancer patients, chronic patients and prevention of multimorbidity in subjects at risk.

Keywords: exercise training and nutrition counseling, psychological well-being, physical activity, technology – ICT, eHealth, prehabilitation, mHealth, behavioral change

INTRODUCTION

Prehabilitation can be defined as a preventive intervention including patient-tailored therapies encompassing optimization of underlying chronic medical conditions, promotion of physical activity and nutritional and psychological support. Prehabilitation programs are designed to optimize the physical and psychological condition of patients undergoing major elective surgery with the final aim to improve clinical outcomes and foster post-surgical functional recovery. The intervention has shown its potential for healthcare value generation in different randomized controlled trials (1–5). However, despite international experts' endorsements (6–10), its implementation as a standard of care within the Enhanced Recovery After Surgery (ERAS) recommendations (11) is still pending.

Limitations of the current evidence on effectiveness of prehabilitation are the heterogeneity among the studies. The patient population enrolled varies greatly, and it is unclear whether all patients benefit or whether only those deemed at higher risk for surgery benefit. Characterization of responders to preoperative exercise training has not been investigated thoroughly and the variety of outcome measures that exist in current literature make comparisons between studies difficult. Despite high intensity exercise training has proven effective (1–3), the type and intensity of exercise training that provides best outcomes is still a controversial hot topic (12). To overcome these well-identified aspects limiting adoption of prehabilitation before major surgery as a routine practice in different healthcare settings, multicenter, international trials with adequate sample size and appropriate power are required.

It is of note, however, that consolidated results of the ongoing PAPRIKA project (2019–21) in Barcelona (13) have identified five actionable areas that seem to play a pivotal role to ensure successful scale-up and sustainability of prehabilitation in the clinical setting. The project clearly indicates the need for: i) Refining the characteristics of the intervention; ii) Building capacity and enhancing service delivery; iii) Risk assessment and personalization; iv) Mature digital support; and, v) Transfer of the service to the community, preserving high-intensity exercise training.

Within this scenario, we believe that digital innovation can facilitate large-scale deployment of successful community-based personalized prehabilitation programs (14–16) by supporting: i) deep remodeling of case management strategies fostering an effective communication and engagement among healthcare professionals, as well as between healthcare professionals and patients and caregivers; ii) effective behavioral change techniques fostering self-efficacy and adherence to community-based interventions (i.e. remote monitoring, goal setting, feedback and educational material, among others); and, iii) decision support system tools for enhanced risk assessment and personalized service selection.

The current manuscript details a proposal to bring digital innovation to novel community-based prehabilitation programs, with special focus on its applicability. The introduction of the Health-Circuit approach will facilitate a "connected experience" for both the patient and the healthcare professionals fostering engagement into the care management process. Moreover, this proposal has the potential to be adopted by programs supporting long-term management of cancer patients (17) and chronic patients, as well as prevention of multimorbidity in subjects at risk. The final milestone would be the optimization of long-term self-management programs with proven health value generation.

DIGITAL INNOVATION ENABLING COMMUNITY-BASED PREHABILITATION

A core aspect to take into account for an optimal management of prehabilitation programs is to foster digital innovation to effectively enable: i) change of management paradigm to support collaborative case management; ii) effective engagement between stakeholders by customizable and interoperable tools providing communication and information sharing between all stakeholders to avoid fragmentation of care; iii) compliance with data security and privacy regulations; iv) customizable and interoperable integrated care pathways facilitating personalization of the service and effective engagement among stakeholders; v) remote monitoring (i.e. physical activity, physiological signs and patient-reported outcomes and experience measures, among other aspects) to support patient adherence to the program, empowerment for self-management and promotion of healthy lifestyles; and, vi) the use of health risk assessment tools supporting decision making, preventive medicine and monitoring of key performance indicators.

It is important to highlight that continuous and precise telemonitoring of patients under the umbrella of a prehabilitation program, merged with traditional perioperative assessment variables (i.e. American Society of Anesthesiologists risk score (18), GLIM criteria for the diagnosis of malnutrition (19), pre-albumin), is a promising source of comprehensive information to be analyzed in an integrative manner by computational models in order to enhance surgical risk assessment and stratification to potentially characterize responders and inform personalized service selection. The digital innovation to community-based prehabilitation programs presented in the current manuscript, and currently being developed at Hospital Clínic de Barcelona (HCB), proposes the use of smart and adaptive case management (20) tools shaping a common digital ecosystem among stakeholders without requiring tight integration with existing electronic medical records. This adopted health-system approach allows better coordination among specialized teams (i.e. surgery, anesthesiology, oncology, physical therapy) within the hospital, as well as vertical (with primary care) and horizontal integrations (i.e. primary care, health clubs, sport centers) to constitute a functional prehabilitation unit that proactively establishes co-designed work plans, trusted conversations, and exchanges relevant case data. Therefore, the digital support aims to tighten engagement of professionals with care coordination activities optimizing both value and costs (i.e. LEAN approach) (21) promoting an active role of patients thanks to an artificial intelligence-supported, cloud-based, and general data protection regulation

(GDPR)-compliant communication channel (professionals' backend). Moreover, it also includes a mobile app to allow the prehabilitation team to communicate among them and with patients, which results in higher service effectiveness and fewer unplanned events.

The aforementioned approach to community-based prehabilitation programs leverages the Catalan best practice in digitally-enabled person-centered care (22) and the results of the EIT-Health supported innovation project PAPRIKA (2019–21) (13). PAPRIKA offers a prototyped and piloted digital health platform, co-designed by healthcare professionals along with prehabilitation patients and caregivers. Main functionalities of the digital health platform are summarized in **Figure 1** and are also discussed below.

Functionalities of the Professionals' Backend

The professionals' backend allows the prehabilitation team members to prescribe and monitor the tasks status for patients' self-management, including: i) advices for enhanced management of multimorbidity; ii) physical activity goals; iii) nutritional advices; iv) mindfulness exercises in audio format; v) consulting images for the nutritional diary; and, vi) predefined data collection instruments (i.e. hospital anxiety and depression scale, Borg scale). Moreover, prehabilitation professionals have access to a multimedia chat to communicate with patients, which is planned to evolve towards a patient-centered communication channel for remote patient consultation (tele- or videoconferencing) and remote teamwork among professionals (i.e. clinical case discussion, team coordination).

In terms of adaptive case management features, the professionals' backend currently supports a work-flow engine that allows the creation from scratch and edition of prehabilitation work-plans, which can be customized with specific data collection instruments and periodic notifications to facilitate patient engagement. It is important to highlight that the professionals' backend can use a HL7-FHIR middleware for standard-based integration with site-specific electronic medical records (i.e. SAP®) and electronic case report form (eCRF) for real-world cohorts [i.e. REDCap® (23)]. However, it is designed to operate on top of existing health information systems, without tight integration requirements. Health Information Exchange is expected to take place within patient-centered conversations when considered necessary by healthcare professionals.

Functionalities of the Mobile App

The mobile app provides patients access to a follow-up timeline to check-out their daily/weekly evolution of prehabilitation goals and achievements. Moreover, Bluetooth connectivity with physical activity trackers facilitates the follow-up of physical activity goals.

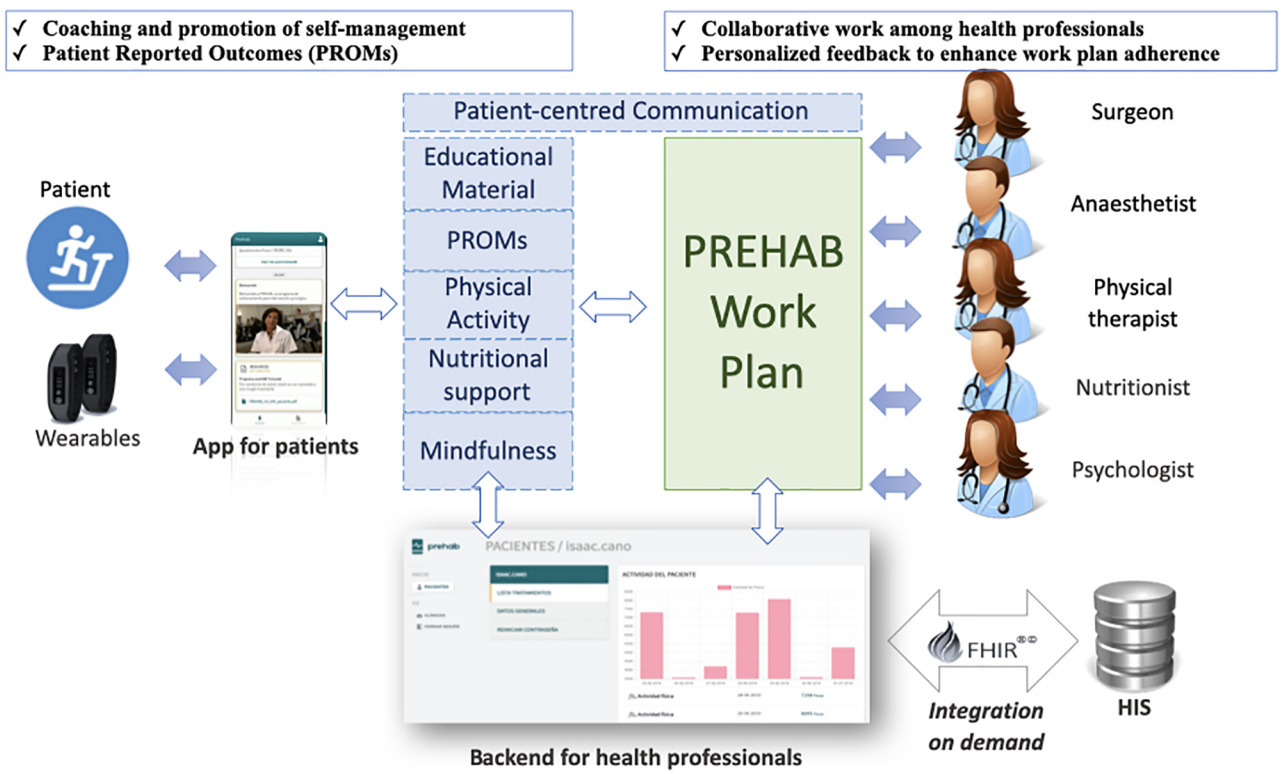

FIGURE 1 | General description of the Health-Circuit approach adopted by the integrated set of smart and dynamic case management tools (PREHAB) of the EIT-Health supported innovation action PAPRIKA (2019–21). FHIR, Fast Healthcare Interoperability Resources; HIS, Hospital Information System.

In terms of communication, patients have a bidirectional messaging functionality supporting both text and images. Moreover, patients can also access predefined educational material in portable document format (PDF) and video formats and answer predefined data collection instruments to report their outcomes and/or experiences. The mobile app for patients is also planned to evolve toward a patient-centered communication channel for remote patient consultation (tele- or videoconferencing).

MAIN CHALLENGES FOR DIGITAL INNOVATION IN SURGICAL PREHABILITATION

Compared to other sectors, healthcare (and in turn in surgical prehabilitation) has traditionally been slower in adopting digitalization. Based on the outcome of a recent state-of-research analysis (24) three potential answers could be found as to why the healthcare industry is lagging behind other sectors in its digital transformation. Firstly, researchers refer to concerns around data security that lead to patients' rejection, as well as regulatory barriers for data use. Second, although health risk assessment is considered to enhance personalized and predictive medicine, its design and implementation is linked to complex processes that require specific expertise in data analytics. Third, healthcare professionals partly hinder further patient empowerment, mainly because of operational changes required to manage novel-patient centered value-based interventions. However, the ongoing COVID-19 pandemic is demonstrating the urgent necessity for the digital transition in the healthcare system (25–27).

In the prehabilitation arena (28, 29), digitalization should facilitate optimization of the service as well as its transference to the community, with special emphasis on a value-based and patient-centered approach appealing for innovative financing solutions. To this end, the Health-Circuit approach described above has three favorable traits. Firstly, building on top of existing health information systems, without requiring tight systems integration, it solves lack of health information exchange generated by health information silos, which often creates frustration among health professionals. A second aspect is that it solved the communication problem with flexibility for the care team: healthcare professionals, patients/careers and the community (e.g. Health clubs, wellness centres, etc.), which should facilitate its use in highly heterogeneous scenarios. Last but not least, this setting acknowledges the key role of co-design, flexibility, and customization as a basic pillar to minimize a professional's resistance to operational changes.

The approach shows high potential for transferability and can lead to enhancement of current strategies for the management of patients with complex chronic conditions, even beyond the perioperative care period. Prehabilitation is raising increasing interest in non-surgical areas like in oncological patients to increase of both functional capacity and resilience before, during and after treatment (30), as well as in frail elderly individuals for prevention of falls. This indicates a potentially high relevance of the approach adopted in Barcelona at both healthcare and societal levels, beyond the specific preoperative focus. Moreover, characteristics of the digital support inherently ensure transferability of methods, digital health tools, and outcomes due to alignment with activities of relevant international societies (i.e. provide an example).

COMMUNITY-BASED PREHABILITATION PROGRAMS: PHYSICAL ACTIVITY AS A USE CASE

Surgical prehabilitation can be defined as a multicomponent that includes personalized preventive interventions aiming to improve a patient's health status to enhance perioperative outcomes. In that sense, it can be conceptualized as a multimodal program to be tailored to each patient's modificable risk factors, in terms of: i) optimization of multimorbidity management; ii) type of modules included (i.e. exercise training, physical activity, nutritional optimization, behavioral cognitive techniques, alcohol and smoking cessation, hemoglobin optimization); iii) total volume of each module taking into account: frequency of treatment administration (i.e. days per week), intensity of each treatment session, time of each single session of treatment administration (i.e. minutes) and total duration of each treatment module (i.e. days or weeks); and, iv) degree and frequency of monitoring the response of each module. As such, the total volume and context for administering each module will be directly connected to a patient's needs, while frequently monitoring the dose-response relationship. As stated in the heading of this section, the current focus is the physical activity component of prehabilitation programs as a use case to exemplify prescription of its volume, monitoring and modularization of the service.

Physical Activity Prescription in a Digital Scenario

There is strong evidence that lower levels of physical activity are related to poor health outcomes (31). Moreover, reduced physical activity increases the possibilities of developing most prevalent chronic conditions (32–37), including cancer (38). Furthermore, a growing body of evidence suggests positive effects of physical exercise on cancer specific as well as all-cause mortality (39, 40). Physical activity is defined as any bodily movement produced by skeletal muscles resulting in energy expenditure, while physical exercise is a subset of physical activity that is planned, structured, repetitive and purposeful. Activities of daily living are another subset of physical activity and this term refers to a set of basic, everyday tasks required for personal self-care and independent living (41). Finally, physical inactivity is a term commonly used to designate a level of physical activity that is below a specified threshold.

As a lower preoperative aerobic capacity is independently associated with worse postoperative outcomes in major abdominal surgery, we are interested in applying the above

mentioned concepts within a prehabilitation program by stimulating both daily physical activity and physical exercise training. As such, the aim is to optimally increase preoperative aerobic capacity, specifically focused at those patients with a low aerobic capacity, in order to improve postoperative patient- and treatment-related outcomes. In that sense, each modality requires a specific type of setting, and promotion, assessment, and evaluation methods and devices as discussed below.

Although the prehabilitation model proposed in the current article is mainly based in the community setting, we consider the realization of a participative group sessions with a behavioral cognitive therapy approach in order to: i) educate on physical activity and physical exercise training performance (i.e. solving doubts, identifying "false myths" on the topic, alarm signs during exercise); ii) co-design the intervention while taking barriers and facilitators into account; iii) enhance a patient's self-efficacy and motivation and commitment with the work-plan; and, iv) educate on the use of the digital solutions supporting the intervention.

In terms of physical activity monitoring, we can divide the existing portable devices in two main groups, namely, pedometers and accelerometers. Firstly, pedometers are devices which measure the number of steps performed in a given period of time and have proven a positive role as a motivational tool to increase physical activity levels (42). On the other hand, accelerometers are portable devices that detect acceleration, thereby reflecting bodily movement that may provide an estimate of time spent above or below a pre-determined physical activity threshold. However, due to higher costs and difficulty with data analysis and management the use of accelerometers is typically limited to research. In contrast, pedometers are more user-friendly, cheaper and, thus, more likely to be adopted for clinical and real-world applications. In the prehabilitation field, a pedometer-based physical activity plan seems as an interesting module to include in multimodal prehabilitation programs (3, 4, 43, 44), especially to complement high-intensity exercise training modules. In terms of tailoring pedometer-based programs, there are well-established values that can be used as a theoretical framework to personalize the amount of steps/day to each type of patient included in prehabilitation (45, 46).

In the community-based physical exercise training scenario, frequently used and accessible tools for monitoring exercise training intensity can be divided in two main groups: heart rate monitors and self-perceived exertion level scales (47). Both tools can be implemented into mobile digital solutions and are also easily managed by patients. Moreover, most of physical activity and heart rate monitoring devices, already available in the market, provide interesting and user-friendly app and web-based interfaces. These interfaces can provide information on patient's work-plan adherence regarding predefined goals, including for example adherence to physical exercise training, symptoms experienced during physical activity, levels of stress (visual analog scales), and daily caloric intake. These valuable features are key to enhance self-efficacy and self-management with a proper interaction with the case manager in order to monitor progression and subsequently re-adjust the goals periodically (i.e. weekly). Moreover, it is important to highlight that, in terms of the community-based setting, we consider not only traditional indoor physical exercise training sessions, but also outdoor low-tech physical activities allowing exercising at high intensity, such as Nordic walking (48, 49). As such, self-administered community-based high intensity training, with the remote follow-up of a physical therapist, is a plausible option to enhance service delivery.

Behavioral Change Techniques and Digital Health

It is well known that aerobic capacity is not a determinant factor related with physical activity levels. In this regard, core components to be included in successful behavioral interventions (i.e. physical activity and nutrition) have been reported in several meta-analyses and guidelines (50–55). Therefore, to design effective digital solution to foster an active lifestyle, it is key to implement well-established behavior change techniques for enhancement of complex behaviors, such as physical activity. Most commonly used behavioral change techniques that appeared effective in eHealth interventions in highly prevalent chronic conditions such as cardiovascular conditions, type 2 diabetes, obesity and chronic pain, among others, are already reported (56–58).

On this basis, it is highly recommendable that mobile apps designed to support community-based physical activity and physical exercise training under the umbrella of multimodal prehabilitation programs include the following functionalities: i) information on health consequences of enhancing physical activity levels by means of personalized education information, likely in a video format; ii) personalized instructions on how to perform physical activity, likely in a video format; iii) weekly goal setting; iv) tools for self-monitoring of physical activity level and intensity, heart rate, and symptoms during its practice; and, v) feedback on performance both, automatic, based on predefined rules and goals, and also by means of direct chat with the physical therapist. Moreover, this approach can be also applied in other modules of the prehabilitation program such as nutritional optimization, psychological management, and/or smoking and alcohol cessation.

CONCLUSIONS

Digital innovation is a cornerstone aspect to consider to successfully enable large scale adoption of community-based prehabilitation with the final aim of enhancing access and adherence to these programs. Technological developments should support collaborative work and engagement between stakeholders by customizable and interoperable tools to avoid fragmentation of care. Moreover, it is key to design eHealth solutions for patients including effective behavioral change techniques in order to optimize clinical outcomes. Finally, the digital approach described in the current manuscript have the potential to be adopted at a population level by long-term self-management and healthy lifestyles promotion programs to enhance medical prognosis for most prevalent

chronic conditions and for prevention of multimorbidity in subjects at risk.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the supplementary material. Further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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Nutrition Care Process Model Approach to Surgical Prehabilitation in Oncology

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The nutrition care process is a standardized and systematic method used by nutrition professionals to assess, diagnose, treat, and monitor patients. Using the nutrition care process model, we demonstrate how nutrition prehabilitation can be applied to the pre-surgical oncology patient.

Keywords: surgical nutrition, oncological nutrition, pre-operative, pre-surgery, pre-habilitation, before surgery

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NUTRITION CARE PROCESS

The nutrition care process model (NCPM) is a standardized and systematic approach that nutrition professionals, namely dietitians (referred to as Registered Dietitians, RDs, in most of Canada and the United Kingdom, and Registered Dietitian Nutritionists, RDN, in the United States), use to provide care (1). The NCPM has been adopted by international dietetic associations and is updated by an international working group every 5 years (2–5). The model follows nutrition screening and consists of four interrelated steps: (1) nutrition assessment, (2) nutrition diagnosis, (3) nutrition intervention and (4) nutrition monitoring and evaluation (1). The first two steps involve problem identification, while the final two steps involve problem solving. The structured framework was designed to enhance quality of care and nutritional status. Indeed, reported benefits of adopting the NCPM include enhanced productivity, improved resolution rate of nutrition-related problems, and improved physician acknowledgment of nutrition recommendations (6).

A recent scoping review of nutrition within prehabilitation oncology research identified that nutrition assessment was inconsistently applied across these studies, interventions did not often meet reference standards, and two-thirds of these studies did not monitor the nutrition intervention nor evaluate nutrition outcomes (7). Given that NCPM represents a global standard for provision of nutrition care, we advocate for its use in prehabilitation and have applied this model to the pre-operative surgical patient to illustrate how nutrition care can be effectively implemented and optimized.

Nutrition Screening

Nutrition screening precedes the NCPM and is the first step in identifying subtle or overt malnutrition. Screening should be applied to all patients with cancer (8). Nutrition screening tools were designed to be administered quickly by non-nutrition professionals to identify patients *at risk of malnutrition*. Patients identified as being "at risk" would trigger a referral to a RD for a comprehensive nutrition assessment and diagnosis of malnutrition. Early screening at the first hospital appointment before surgery, or at minimum by the first surgical visit, using a validated tool, offers the opportunity to intervene with a targeted or specialized nutrition intervention (alone or in combination with other approaches, such as exercise and psychological support/behavior change) that could improve patient outcomes (9). Remedial nutrition therapy for ∼7-14 days before surgery has been found to improve post-operative outcomes (8), including length of stay (10), and serious complications (11, 12). However, some observational evidence suggests that a longer period of nutritional repletion is required to improve parameters of physical functioning in malnourished patients (13, 14). An earlier screen affords greater possibility for nutrition care management and success. Patients who screen negative for malnutrition risk preoperatively should be re-screened if their condition changes or on admission to hospital.

Nutrition screening tools that are commonly used in oncology or surgery settings are listed in **Table 1**. Most of these tools have been validated using "gold standard" nutrition *assessment* tools, used to diagnose malnutrition, including the Subjective Global Assessment (SGA) (37, 38) and the Patient-Generated Subjective Global Assessment (PG-SGA) (39). Appreciation of these screening tools necessitates an understanding of malnutrition. Although there is no accepted definition for malnutrition, the condition can be described as an unbalanced nutritional state, resulting from inadequate nutrient intake and/or altered nutrient requirements related to disease and treatment, that alters body mass, body composition and function (40, 41). Recently, the Global Leadership Initiative on Malnutrition (GLIM) (42) convened to offer expert-consensus on the core criteria to diagnose malnutrition in a clinical setting. This group described the diagnosis of malnutrition as having an etiology and a phenotype. The etiology includes reduced food intake/food assimilation, malabsorption, disease burden/inflammation, and the phenotype is expressed with weight loss, reduced muscle mass, and low body mass index. A diagnosis of malnutrition is based upon the presence of at least one phenotypic criterion and one etiologic criterion.

Table 1 provides a list of nutrition risk screening tools, applies the GLIM criteria to these tools, and presents the psychometric properties of these tools to help the reader select the most appropriate tool for their patient population. Choice of an appropriate nutrition screening tool will depend on local factors including whether validation studies have been completed in the population of interest, sensitivity and specificity to detect malnutrition, prevalence of malnutrition, available resources, ease of completion and capacity for collecting data by healthcare professionals or patients themselves. Ideally a tool should be both highly sensitive and specific; however, a perfect screening tool does not exist. A tool with 75% sensitivity would identify 75% of malnourished patients correctly but 25% of malnourished patients would remain undetected (43). A tool with 75% specificity would correctly identify those *without* malnutrition 75% of the time, but 25% of the time a patient without malnutrition would be falsely labeled as being "at malnutrition risk" and thus referred to the RD for assessment unnecessarily (44). Given that a misdiagnosis of being at risk of malnutrition (i.e., false positive) is relatively benign if resources for a follow-up assessment by an RD are available, use of a highly sensitive tool is desirable. An institution with limited RD resources for follow-up assessment post-screening, however, might consider a tool that is highly specific to reduce the number of non-malnourished patients being referred to the RD for assessment (but in selecting this tool would accept that a portion of malnourished patients will remain undetected). For an excellent review of considerations for selecting screening tools we refer the reader to Elia and Stratton (45).

Nutrition Assessment

Nutrition screening tools do not perfectly identify patients with malnutrition. A highly sensitive tool would correctly identify malnourished patients while a highly specific tool would correctly identify non-malnourished patients (44). Thus, patients who are identified as being at risk for malnutrition must receive a nutrition assessment. Nutrition assessments are conducted by a RD for the purpose of diagnosing malnutrition and other nutrition-related problems. Nutrition assessment is a "systematic approach to collect, classify, and synthesize important and relevant data" (1). RDs use validated malnutrition assessment tools, including the SGA and PG-SGA, to diagnose malnutrition. RDs also perform comprehensive nutrition assessments that involve an evaluation of food and nutrition-related history, anthropometric measurements, biochemical data, health and disease status, psychological and behavioral issues, social and environmental influences, and a nutrition-focused physical exam/functional assessment.

An assessment of food and nutrition-related history includes an evaluation of food records or dietary food recalls to estimate usual nutrient intakes and the adequacy of these intakes. The National Cancer Institute offers an excellent resource on choosing an appropriate tool for estimating usual nutrient intakes (https://dietassessmentprimer.cancer.gov/approach/). Considerations for selection of a dietary tool include whether the goal is simply to describe dietary patterns, assess dietary intake, examine an association, or to evaluate the effect of an intervention. When assessing the effect of an intervention, multiple 24-h recalls are often cited as the best estimate of usual intakes (46). Although new technologies, including mobile apps, may enhance the accuracy of food records (47). If the goal of the intervention is to change behavior, food records could be an appropriate tool to support and track behavior change (48).

An assessment of nutrition-related history also includes an evaluation of nutrition-impact symptoms, including loss of appetite and diarrhea, that impede adequate oral intake. A prospective longitudinal survey of the nutrition-impact symptoms experienced by patients undergoing systemic

TABLE 1 | A list of nutrition risk screening tools and their psychometric properties for use in oncology and surgical settings.

Tool	Phenotype	Etiology	Psychometric properties and intended population
Mini nutritional assessment—short-form (MNA-SF)	Unintentional weight loss Low BMI Low muscle mass	Reduced food intake Disease burden	As far as we are aware, this tool has not been validated against SGA or PG-SGA in surgical or oncological populations. However, this tool has been validated against the full MNA, which is a valid nutritional *assessment* tool used to diagnose malnutrition in older adults, specifically (15).
Malnutrition screening tool (MST)	Unintentional weight loss	Reduced food intake	Mixed cancer types, oncology inpatients, $n = 126$ (16): Sensitivity: 66% Specificity: 83% Positive predictive value: 91% Negative predictive value: 49% (as compared with the PG-SGA) Mixed cancer types, radiation, $n = 106$ (17); chemotherapy, $n = 50$ (18) and $n = 246$ (19); chemotherapy or supportive cancer care, $n = 201$ (20); outpatients, $n = 300$ (21): Sensitivity: 70.6-100% Specificity: 69.5-92% Positive predictive value: 40-59% Negative predictive value: 99-100% [as compared with the PG-SGA (18, 19, 21), SGA (17, 20)] Cancer and non-cancer, surgical inpatients, preoperative evaluation, $n = 100$ (22): Sensitivity: 54% Specificity: 25% Kappa coefficient: 0.90 (as compared with the SGA)
Malnutrition universal screening tool (MUST)	Unintentional weight loss Low BMI	Reduced food intake Disease burden	Mixed cancer types, radiation outpatients, $n = 450$ (23); chemotherapy outpatients, $n = 100$ (24): Sensitivity: 80-86.7% Specificity: 89-94.5% Positive predictive value: 87-92.9% Negative predictive value: 100-89.7% Kappa coefficient: 0.79-0.86(as compared with the PG-SGA) Colorectal cancer, surgical inpatients, preoperative assessment, $n = 45$ (25): Sensitivity: 96% Specificity 75% Positive predictive value: 82.8% Negative predictive value: 93.8% Kappa coefficient: 0.7(as compared with the SGA) Cancer and non-cancer, surgical inpatients, preoperative assessment, $n = 300$ (26), assessment performed within 36 h of admission, $n = 120$ (27): Sensitivity: 67.8-85% Specificity: 93-94.4% Positive predictive value: 76-89% Negative predictive value: 91.9-99%(as compared with the SGA) Cardiac, surgical inpatients, preoperative assessment, $n = 894$ (28): Sensitivity: 97.9% Specificity: 87.1% Positive predictive value: 29.7% Negative predictive value: 99.9%(as compared with the SGA)
Nutritional risk screening-2002 (NRS-2002)	Unintentionalweight loss Low BMI	Reduced food intake Disease burden	Head and neck/CNS cancer, oncology outpatients, $n = 124$ (29): Sensitivity: 67.5% Specificity: 92.9% Positive predictive value: 97.7% Negative predictive value: 68.4% Kappa coefficient: 0.71(as compared with the SGA) Gastric cancer, surgical inpatients, assessment performed within 24 h of admission, $n = 80$ (30): Sensitivity: 80% Specificity: 96% Kappa coefficient: 0.69(as compared with the SGA) Cancer and non-cancer, surgical inpatients, preoperative assessment, $n = 300$ (26), assessment performed within 36 h of admission, $n = 120$ (27): Sensitivity: 60.7-80% Specificity: 89-96.3% Positive predictive value: 80.9-87% Negative predictive value: 90.4-100%(as compared with the SGA)

(Continued)

TABLE 1 | Continued

Tool	Phenotype	Etiology	Psychometric properties and intended population
Short nutrition assessment questionnaire (SNAQ)	Unintentional weight loss	Reduced food intake	Cardiac, surgical inpatients, preoperative assessment, $n = 894$ (28): Sensitivity: 91.5% Specificity: 87.5% Positive predictive value: 28.9% Negative predictive value: 99.5% (as compared with the SGA)
Canadian nutrition screening tool (CNST)	Unintentional weight loss	Reduced food intake	Inpatients, (on admission) 22% of sample surgical, $n = 123$ (31): Sensitivity: 72.9% Specificity: 85.9% Positive predictive value: 82.7% Negative predictive value: 77.5%(as compared with the SGA)
Royal Marsden Nutrition Screening Tool (RMNST)	Unintentional weight loss Underweight appearance	Reduced food intake Reduced food assimilation	Mixed cancer types, oncology inpatients, $n = 126$ (16): Sensitivity: 93% Specificity: 53% Positive predictive value: 83% Negative predictive value: 76%(as compared with the PG-SGA)
Abridged patient-generated subjective global assessment (aPG-SGA)	Unintentional weight loss	Reduced food intake Reduced food assimilation	Mixed cancer types, oncology outpatients, $n = 246$ (19), $n = 300$ (32), $n = 90$ (33): Sensitivity: 80.4-96.9% Specificity: 72.3-86.2% Positive predictive value: 45% (19) Negative predictive value: 98% (19) Kappa coefficient: 0.49 (19)[as compared with PG-SGA (19, 32) and the SGA (33)]
NUTRISCORE	Unintentional weight loss	Reduced food intake Reduced food assimilation	Mixed cancer types, oncology outpatients, $n = 394$ (34): Sensitivity: 97.3% Specificity: 95.9% Positive predictive value: 84.8% Negative predictive value: 99% Area under the curve: 0.95(as compared with the PG-SGA)
Bach Mai Boston Tool (BBT)	Unintentional weight loss Low BMI	Reduced food intake	Mixed cancer types, oncology outpatients, $n = 270$ (35): Sensitivity: 67.1% Specificity: 94.4% Positive predictive value: 93.3% Negative predictive value: 70.9% Area under the curve: 0.81 Kappa coefficient: 0.6(as compared with the PG-SGA)
Malnutrition screening tool for cancer (MSTC)	Unintentional weight loss Low BMI	Reduced food intake	Mixed cancer types, oncology inpatients, $n = 1{,}057$ (800 for development, 257 for validation) (36): Sensitivity: 94% Specificity: 84.2% Positive predictive value: 67.8% Negative predictive value: 97.6% Area under the curve=0.95 Kappa coefficient: 0.7(as compared with the PG-SGA)
Perioperative nutrition screen (PONS)	Unintentional weight loss Low BMI	Reduced food intake Disease burden	As far as we are aware, this tool has not been validated against SGA or PG-SGA in surgical or oncological populations

BMI, body mass index; CNS, central nervous system; PG-SGA, Patient Generated Subjective Global Assessment; SGA,Subjective Global Assessment.

anti-cancer treatment (SACT) identified that three-quarters experienced at least 1 symptom that affected food intake, including dry mouth, nausea and constipation, within 1 and 6 months of starting chemotherapy and nearly half of these patients continued to experience symptoms 12 months later (49).

Biochemical assessments for nutritional status are largely non-specific and, as a result, nutrition diagnoses are rarely based on biochemical data alone, but rather should be used as a complement to a thorough examination (50). Hypoalbuminemia (low serum albumin concentration), for instance, is not necessarily indicative of malnutrition (i.e., a reduced synthesis of albumin due to reduced substrate availability) because this plasma protein is a negative acute phase reactant that is affected by several conditions including cancer. Albumin also has a long half-life, and thus does not reflect acute changes in nutritional status. However, albumin is predictive of morbidity and mortality (50). While prealbumin (the precursor to albumin) is also a negative acute phase reactant, its pool is smaller and its half-life is shorter, which might make it a more reliable indicator of nutritional status in patients without inflammation (e.g., elevated c-reactive protein) (50). However, few studies have evaluated its relevance in predicting patient prognosis. As such, prealbumin

has not been recommended for the diagnosis of malnutrition (51). C-reactive protein is a commonly used inflammatory marker with several prospective studies suggesting it predicts mortality in cancer (52).

An evaluation of glycated hemoglobin (HbA1c) might be beneficial in patients with and without diabetes. A systematic review of non-diabetic surgical patients identified that 34% of this heterogenous sample had sub-optimal preoperative glycemic control (53) and several observational studies in pre-surgical patients without cancer have suggested that there is a link between preoperative glycemia and postoperative outcomes (53–55). Fructosamine (another index of glucose homeostasis) has a shorter half-life than HbA1c, and thus might be useful for the assessment of acute changes in the short period before surgery (56). Other biochemical assessments to consider include serum levels of micronutrients, such as 25-hydroxyvitamin D (57). Finally, many patients present to surgery with anemia, which is associated with higher rates of morbidity and mortality (58). Several recent reviews have suggested that correction of iron deficiency anemia with iron therapy should take place in the pre-operative/preadmission clinic as a standard component of medical optimization (58, 59). For this reason, integration of prehabilitation programs within pre-operative clinics is recommended (59).

An anthropometric assessment of weight (including weight change), height, and waist circumference are vital components of the comprehensive nutrition assessment. Additionally, body composition assessment has emerged as a crucial component in the evaluation of patients' nutritional status (60). For an excellent review of the methodologies and techniques available for body composition assessment please see Prado and Heymsfield (61). Bioelectrical impedance, when conducted using standardized methods, is often cited as a reasonable option for estimating body composition in a clinical setting, especially in the assessment of change over time (62).

Indirect measures of nutrition status include assessment of strength and function. Malnutrition incites adaptive mechanisms that reduce basal metabolic rate and diminish physical performance in an attempt to conserve nutrient reserves (63). As a result, reduced strength and function are associated with malnutrition status. For instance, using a standard protocol to measure handgrip strength [grip measured three times with a 15 s break between trials (64)], a malnourished patient might exhibit low age- and sex-specific strength or poor recovery between measurements (i.e., a drop in strength with each consecutive measurement) (64). Common methods for testing physical function include the 6-min walk test, gait speed, Short Physical Performance Battery, timed up and go, and 30-s sit-to-stand (62, 65).

Nutrition Diagnosis

Collected data from the nutritional assessment are compared against accepted standards, expert recommendations, and/or patient-defined goals to ascertain nutritional status (1). The aforementioned information, together with the patient's medical and social history, is used to diagnose nutrition-related problems that can be solved by the RD.

Table 2 lists surgery and oncology-specific accepted standards and/or recommendations from several nutrition associations, including the European Society for Clinical Nutrition and Metabolism (ESPEN). We have limited this list to general recommendations and guidelines in surgery and oncology, but the reader should be aware that many disease-specific standards also exist (75). Unfortunately, accepted nutrition guidelines are not often used in prehabilitation (7). A scoping review of 37 prehabilitation studies with a nutrition treatment component in oncology identified that only half of these studies ($n = 21$) specified a goal for their nutrition intervention; of these, 67% ($n = 14$) referenced the stated goals and only 43% ($n = 9$) used a reference standard or accepted guideline, including ESPEN guidelines (7). The potential to improve patient outcomes is limited unless clinical guidelines are followed (76).

Based on the comprehensive nutritional assessment, the RD identifies a nutrition-related problem that can be treated (1). This diagnosis is expressed using standardized language by labeling the identified problem, citing the etiology of the problem, and providing evidence of the problem (i.e., signs and symptoms). Malnutrition is a common nutrition diagnosis pre-surgery. The prevalence of malnutrition in oncological patients is reported to range from 10 to 85% (77), depending on the definition of malnutrition, assessment tool, tumor-type, cancer stage, and adjuvant/neoadjuvant treatments (78). An example diagnostic statement pre-surgery is as follows: severe chronic malnutrition (problem) related to nutrition-impact symptoms, including constipation, early satiety and fatigue (etiology) as evidenced by meeting 65% of estimated protein requirements, 10% weight loss in past 6 months, and low handgrip strength. Other common nutrition diagnoses pre-surgery include inadequate oral intake, inadequate protein energy intake, impaired nutrient utilization, altered gastrointestinal function, unintended weight loss, underweight, and food and nutrition related knowledge deficit. Although not part of the NCPM standard terminology, a diagnosis of sarcopenia, which can occur independently of malnutrition (41, 79), is also an important nutrition-related diagnostic consideration given the catabolic impact of surgery. Sarcopenia in cancer can be primary (aging related), secondary (disease related) or both. These differences are important as primary sarcopenia is defined as depleted muscle mass and strength, while secondary sarcopenia is defined as only a measure of depleted muscle mass [the latter is an approach used in the vast majority of oncology-related publications on the topic (79, 80)].

Nutrition Intervention

The NCPM defines a nutrition intervention as "a purposefully planned action(s) designed with the intent of changing a nutrition-related behavior, risk factor, environmental condition, or aspect of health status" (1). The nutrition intervention is designed to improve or resolve the nutrition diagnosis/problem. If it is not possible to resolve the diagnosis or its etiology, the nutrition plan is aimed at relieving signs and symptoms. Importantly, for patients who have been assessed by an RD and diagnosed with a nutrition problem, there is no "one-size-fits-all" approach to resolve the problem. Instead, the comprehensive nutrition assessment and diagnosis are used to

TABLE 2 | Clinical nutrition guidelines for surgery and/or oncology patients.

Organization	Energy requirements	Protein requirements	Screening/assessment tool
European society of enteral and parenteral nutrition (ESPEN)			
Oncology (66)	25-30 kcal/kg/day	>1-1.5 g/kg/day	Screening: NRS-2002, MUST, MST Assessment: SGA, PG-SGA, MNA
Surgery (8)	25-30 kcal/kg/day	1.5 g/kg/day	Screening: NRS-2002 Assessment: SGA
Clinical oncology society of Australia (COSA) (67)	25-30 kcal/kg/day	1-1.5 g/kg/day	MST, MUST, MSTC, abPG-SGA
French Speaking Society of Clinical Nutrition and Metabolism (SFNEP) (68)	30-35 kcal/kg/day	1.2-1.5 g/kg/day	All patients: PG-SGA, SGA Geriatric patients: MNA
Polish societies of: surgical oncology, oncology, clinical oncology and parenteral, enteral nutrition and metabolism (69)	25-35 kcal/kg/day 35-45 kcal/kg/day (severe cachexia)	0.8-1.5 g/kg/day 2-3 g/kg/day (severe cachexia)	SGA, NRS-2002, MUST Geriatric patients: MNA
Spanish society of medical oncology (SEOM) (70)	25-30 kcal/kg/day	1.2-1.5 g/kg/day	Outpatients: MUST Inpatients: NRS-2002 Geriatric patients: MNA-SF In/outpatients: assessment MST PG-SGA
Oncology evidenced-based nutrition practice guidelines for adults (71)	No recommendation	No recommendation	Inpatient: MST, MSTC, MUST Outpatient: MST
Nutritional support and parenteral nutrition in cancer patients: an expert consensus report (72)	25-30 kcal/kg/day	1-2 g/kg/day 1-1.2 g/kg/day for patients with acute/chronic renal failure	MST, PG-SGA
American Society for Enhanced Recovery and Perioperative Quality Initiative (73)	25-30 kcal/kg/day	>1.2-2.0 g/kg/day	PONS
Enhanced recovery after surgery society (ERAS) and the European society of surgical oncology (ESSO)-Gastrointestinal cancers (74)	25-30 kcal/kg/day	1.5 g/kg/day ideal body weight	PG-SGA

abPG-SGA, abridged scored Patient Generated Subjective Global Assessment; MNA, Mini Nutritional Assessment; MSTC, Malnutrition screening tool for cancer; MUST, Malnutrition universal screening tool; NRS-2002, Nutritional risk screening-2002; PG-SGA, Patient Generated Subjective Global Assessment; PONS, Perioperative nutrition screen; SGA, Subjective Global Assessment.

guide a personalized intervention. As an example, a diagnosis of "inadequate oral intake related to nausea" would require an intervention to improve the diagnosis of inadequate oral intake based on treating its etiology of nausea, and with consideration of the patient's own goals, food preferences, capacity to prepare meals, food and nutrition knowledge, health literacy, and motivation to change.

The first principles and guidance for the conduct of multimodal prehabilitation in cancer were released in 2019 by Macmillan Cancer Support, the Royal College of Anaesthetists and the National Institute of Health Research Cancer and Nutrition Collaboration; this guideline proposed that prehabilitative care should be delivered on a risk-stratified basis to use resources wisely (81). Using this approach, each patient's level of care is based on whether their assessment revealed that a minimal (targeted) intervention or a more intensive (specialist) intervention is needed. Using our experience with prehabilitation (14), we have modified the risk stratified diagram to suit nutrition prehabilitation (**Figure 1**). A patient who has been screened (using tools listed in **Table 1**) and is not at risk of malnutrition or has been assessed by a RD and is not malnourished (i.e., SGA A or PG-SGA < 4), would not require further assessment, diagnosis, and personalized treatment by a RD. Instead, these patients require a universal, non-specialized level of nutrition care to maintain nutritional status. This might look like standardized instructions to meet energy, macro- and micro-nutrient requirements delivered through a handout and/or group class. Patients identified with moderate or suspected malnutrition (SGA B or PG-SGA 4-8), require a short-personalized session with a RD or trained perioperative clinician to provide targeted care based on the specific nutrition-related symptoms (e.g., nausea) that are impeding oral intake. These targeted interventions often require nutrition tips and medical management to sufficiently relieve symptoms to encourage adequate intake. A patient with severe malnutrition (SGA C or PG-SGA ≥ 9) would receive

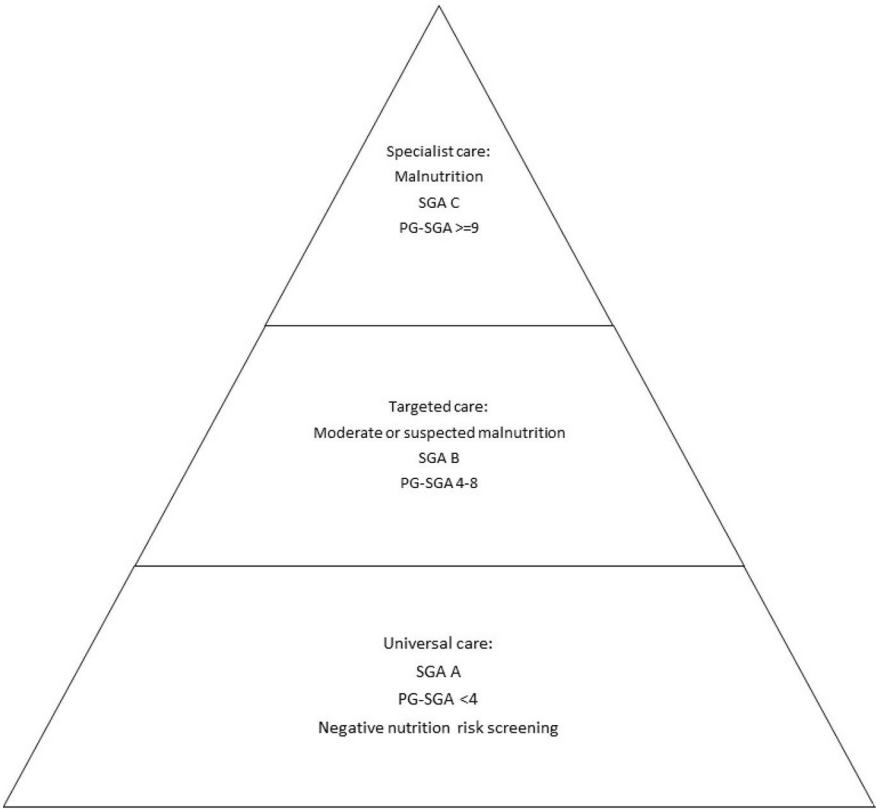

FIGURE 1 | Risk stratified care for nutrition prehabilitation.

a primary, specialized, one-on-one counseling session and nutrition intervention by a RD. The patient's unique nutrition diagnoses dictate the nutrition intervention. At this stage, nutrition support, including oral supplementation, enteral tube feeding, and parenteral nutrition, is almost always required to optimize nutritional intake in the short window of opportunity before surgery.

In addition to preventing malnutrition and correcting nutrition-identified problems, the nutrition component of a multimodal prehabilitation program should work in synergy with the exercise intervention to support optimal gains in mass, strength, physical fitness, and recovery (10, 40, 82). While resistance exercise is regarded as the main anabolic stimulus, nutrition, including adequate dietary protein, provides the necessary substrate to achieve anabolic gains (83). For a review of nutrition within surgery, we refer the reader to Gillis and Carli (84), for nutrition prehabilitation see Gillis and Wischmeyer (40), and for treating low muscle mass see Prado et al. (85).

Monitor/Evaluate

Relevant outcome/indicators need to be measured to evaluate whether the nutrition prescription is appropriate and to determine whether progress has been made toward resolving the nutrition diagnosis (1). Estimated protein requirements, for instance, range from 0.8-3 g/kg (**Table 2**). This is a wide range that requires monitoring to determine whether the prescribed dose is adequate. This step also provides an opportunity to identify barriers [e.g., COM-B questionnaire (86)] and facilitators to support progress, and review/develop new nutrition goals and interventions with patients.

Selection of appropriate outcome/indicators is based on the nutrition diagnosis. As an example, a diagnosis of "inadequate oral intake related to nausea as evidenced by meeting only 50% of estimated energy requirements and 5% weight loss in 1 month" can be monitored with food records and regular weight measurements (see section on Nutrition Assessment) to determine if the diagnosis of inadequate oral intake has worsened, improved, or resolved. Intake-related indicators include nutrient adequacy (e.g., percent energy and protein requirements met), changes in dietary patterns [e.g., healthy eating index (87)], and compliance to prescribed supplements. Biomarkers and biochemical indices can be used to complement intake data. For instance, fructosamine can be used to monitor glycemic control and urinary nitrogen can be used to corroborate protein intake from food records (88). Clinical-related indicators include changes in weight, waist circumference, body composition, and physical function. Patient-related factors include changes in quality of life and knowledge/attitudes related to food and nutrition.

At the targeted level, telephone calls to troubleshoot barriers and asking patients to self-monitor weight can be appropriate. At the specialist level, however, patients require close monitoring and re-assessments so that the nutrition prescription can be modified if it is not adequately meeting patient needs or reaching expected outcomes. While an ideal timeframe for follow-up is unknown, prehabilitation research tends to follow patients weekly or bi-weekly given the short window of opportunity before surgery.

APPLYING THE NUTRITION CARE PROCESS MODEL TO SURGICAL PREHABILITATION

Herein, we present three case studies that apply the NCPM to the pre-surgical oncology patient.

Universal Level of Care

A 65-year-old female presented to her surgeon's office with gynecological cancer. NRS-2002 indicated no recent changes in dietary intake nor changes in weight status (NRS score: 2). Patient was not flagged as having malnutrition risk and thus did not require a RD assessment. To mitigate any future perioperative malnutrition, patient was invited to attend a regularly scheduled weekly pre-operative class that focused on optimizing nutritional intake throughout the perioperative period (before surgery, while in hospital stay, and recovering well at home). The patient was provided information on self-screening and monitoring for malnutrition risk, balanced meals, sample meal plans, and tips to manage common perioperative nutrition-impact symptoms.

Targeted Level of Care

Assessment: Referral received from preadmission clinic for 59-year-old male diagnosed with colon cancer and duodenal invasion at malnutrition risk (NRS 2002:3). Patient experienced an unintended weight loss of ∼3% of his usual stated body weight over the previous month with no weight stabilization. Body mass index classification of overweight status (29.2 kg/m^2). Total estimated energy and protein intake in 24 h was 74 and 63% of estimated needs, respectively. Patient described inadequate oral intake over the preceding month because of several nutrition-impact symptoms including abdominal pain, diarrhea, reduced appetite, and early satiety. Patient described feeling fatigued, especially upon exertion. Baseline functional assessment indicated that he was physically fit: +0.7 handgrip strength z-score [age and sex-specific z-score (89)], 92% of predicted 6MWT (90) based on age and sex, and 22.5 kg/m^2 fat-free mass index [<17.0 kg/m^2 for males indicates reduced fat-free mass (42)]. RD identified that patient is moderately malnourished (SGA: B).

Diagnosis: Inadequate oral intake related to abdominal pain, diarrhea, poor appetite, and early satiety as evidenced by meeting 74% of estimated energy needs, meeting 63% of estimated protein needs, and an unintended 3% weight loss over preceding month.

Intervention: Patient to meet 25 kcal/kg and a minimum of 1.0–1.2 g protein/kg through food intake [ESPEN guidelines (66)]. RD met with patient to assess nutrition knowledge and willingness to change behavior. Patient was provided with targeted dietary tips and handouts to address stated nutrition-impact symptoms and encouragement to support adequate oral intake. Patient-agreed goals: stabilize weight as well as maintain physical fitness and fat-free mass.

Monitor/Evaluation: Follow-up by telephone within 7–10 days to evaluate status of nutrition impact symptoms and oral intake. If nutrition-impact symptoms continue to impede adequate food intake, will assess for oral nutrition supplements (ONS) and medical management of symptoms. Patient to self-monitor weight weekly, if weight does not stabilize, will schedule for one-on-one counseling with a RD.

Specialist Level of Care

Assessment: Referral received from hepato-pancreato-biliary consultant clinic for 78-year-old female with pancreatic ductal adenocarcinoma at malnutrition risk (MUST score: 4). Patient experienced 19.7% unintended weight loss over 2 months. Body mass index classification of normal weight status (23.6 kg/m^2). Total estimated energy and protein intake in 24 h was 66 and 43%, respectively. Patient described inadequate oral intake over preceding month because of several nutrition-impact symptoms, including loss of appetite, nausea, taste changes, aversion to food smells, and early satiety. Patient described pale, greasy, oily stool with occasional bloating. Biochemical data indicated low serum vitamin D (18.9 nmol/L; reference value: >50 nmol/L), zinc (6 umol/L; reference value: 10-22 umol/L) and selenium (0.2umol/L; reference value: 0.8-1.5 umol/L). Nutrition-focused physical exam suggested temporalis muscle wasting. Patient described physical limitations, including spending most of day in bed/chair over the past month. Baseline functional assessment was indicative of deficits: −2.0 handgrip strength z-score [age and sex-specific z-score score (89)] and <10 sit-to stands in 30 s [below population norms for age and sex (91)]. RD identified that patient is severely malnourished (SGA:C).

Diagnosis: (1) Severe acute malnutrition related to no appetite, nausea, taste changes, aversion to food smells, early satiety and malabsorption as evidenced by SGA C category, severe weight loss, inadequate protein energy intake, temporalis muscle wasting, and low physical function; (2) Altered gastrointestinal (GI) function related to inadequate pancreatic enzyme replacement therapy as evidenced by steatorrhea and occasional abdominal bloating.

Intervention: Patient to meet minimum of 25 kcal/kg and 1.2 g protein/kg through food intake and oral nutrition supplements [ESPEN guidelines (66)]. RD assessed nutrition knowledge and willingness to change behavior. RD addressed nutrition impact symptoms and encouraged high protein high energy diet through one-on-one counseling. A motility agent was prescribed and instructed to be taken 30 min before meals. Patient was encouraged to consume ONS twice daily (providing an additional 40 g protein and 800 kcal to meet estimated deficit). RD prescribed multivitamin/mineral and vitamin D replacement. Pancreatic enzyme replacement therapy

initiated, and education/handouts provided. Patient agreed goals: stabilize/gain weight, improve physical function, improve GI function and nutrient absorption.

Monitor/Evaluate: Patient to record food intake for 3 days (1 weekend day and 2 weekdays) and will reassess total caloric, protein, and ONS intake in 1 week by telephone. Patient to self-monitor weight weekly. Pancreatic enzyme replacement therapy questionnaire and GI symptom rating scale will also be evaluated over telephone in 1 week. Follow up visit scheduled before surgery to re-assess weight, physical function, and readiness /appropriateness to proceed with surgery.

CONCLUSION

We have demonstrated, using the nutrition care process, how early coordinated action from surgical and dietary departments can provide optimal nutrition care to pre-surgical patients. Importantly, the NCPM provides a framework to guide professional nutrition practice. Given the recent scoping review of nutrition within prehabilitation research (7), which indicated that many nutrition interventions are currently conducted without reference to best practice guidelines, we suggest that implementation of the systematic NCPM could enhance the contribution of nutrition to prehabilitation and improve patient outcomes.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to the manuscript including editing and approval of the final manuscript.

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The Clinical Value of Pulmonary Rehabilitation in Reducing Postoperative Complications and Mortality of Lung Cancer Resection: A Systematic Review and Meta-Analysis

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Background: Pulmonary rehabilitation is one meaningful way of improving exercise tolerance and pulmonary function. Thus, it may reduce the postoperative complications and mortality of pulmonary resection. Hence, we refreshed the data and conducted this systemic analysis.

Method: We searched Pubmed, Web of Science, and EMBASE using "lung OR pulmonary" AND "operation OR resection OR surgery" AND "rehabilitation or exercise." The cut-off date was September 30, 2020. The publications were filtrated, and data were extracted from all selected studies by two reviewers. Review Manger 5.1 and the fixed or random regression model were used for calculating the pooled odds ratio (OR).

Result: Finally, 13 publications were enrolled in this study. Among them, five publications reported mortality, nine reported postoperative complications, and seven reported postoperative pulmonary complications. The pooled OR of mortality was 1.32 [95% confidence interval (CI): 0.54–3.23] for the pulmonary rehabilitation group, the pooled OR of postoperative complications was 0.62 (95% CI: 0.49–0.79) for the pulmonary rehabilitation group, and the pooled OR of postoperative pulmonary complications was 0.39 (95% CI: 0.27–0.56) for the pulmonary rehabilitation group. Subgroup analysis revealed the perioperative pulmonary rehabilitation was the most important part.

Conclusion: Pulmonary rehabilitation may not affect the mortality of pulmonary resection patients, however, it could decrease the number of postoperative complications, especially pulmonary complications. Perioperative pulmonary rehabilitation was the most important part of the program.

Keywords: pulmonary rehabilitation, pulmonary resection, postoperative complications, mortality, meta-analysis

Lung cancer was the most leading cause of cancer-related deaths in China and even around the World (1, 2). Among all cases of lung cancer, 80% were non-small cell lung cancer (NSCLC) (3). Radical operation was a valuable way for early-stage NSCLC patients in multidisciplinary team (4). Usually, lung cancer patient characteristics include old age (5), having a history of smoking, and suffering from cardiovascular or respiratory comorbidities (6). These characteristics were also known as negative impactors in surgical tolerability, and they increase the perioperative risk (7). Under current surgical techniques and nursing skills, postoperative pulmonary complications (PPCs) occurred in 20–30% of patients (8). PPCs were regarded as the main causes of prolonged length of hospital stay, increased hospitalization cost, and poor life quality.

Pulmonary rehabilitation was a meaningful intervention in the management of chronic obstructive pulmonary disease or other chronic respiratory diseases (9). In 2015, "An Official American Thoracic Society/European Respiratory Society Policy Statement: Enhancing Implementation, Use, and Delivery of Respiratory rehabilitation" defined pulmonary rehabilitation as "comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors" (10). So, a well-designed pulmonary rehabilitation program should include exercise training, pharmacotherapy, smoking cessation, nutritional support, behavior change, health education, etc. (11). The National Institute of Health and Clinical Excellence guidelines on lung cancer also emphasized the need for rehabilitation programs before and after surgery, stating that the outcomes should include mortality, pulmonary complications, pulmonary function, etc. (12). This topic was frequently studied. Several studies had reported the clinical value of pulmonary rehabilitation in shortening the length of hospital stay and improving exercise tolerance (13–15). At the same time, there had been other studies not showing positive effects of pulmonary rehabilitation program (16, 17). Also, some systemic analyses tried to answer the question of the clinical significance of pulmonary rehabilitation during the peri-operative period (18–22). However, some studies only included a randomized controlled trial (RCT) for future calculation (22). In addition, the newest one was published in 2019, and it only enrolled the publications before June 2017 (21). In the last few years, some new pulmonary rehabilitation clinical trials have been reported, including some non-RCT trials.

Thus, in this study, we aim to update the records and conduct this systemic analysis to explore the clinical value of pulmonary rehabilitation in decreasing postoperative complications and mortality of pulmonary resection.

METHODS

Literature Search

We carried out a computerized search of published research studies in the Medline, Embase, and Web of Science databases and the Cochrane Library with the following: "lung OR pulmonary" AND "operation OR resection OR surgery" AND "rehabilitation or exercise." Alternative spellings and abbreviations were also considered. Reference lists of included studies and relevant reviews were also manually searched. The literature search was conducted without any limitations. The publication date boundaries were January 1, 2005, and September 30, 2020.

All publications in English were considered. Conference abstracts or letters to editors were excluded due to their limited data. No minimum number of patients for a study was required to be included in our meta-analysis.

Inclusion Criteria and Exclusion Criteria

All potentially relevant studies that met the following criteria were retrieved and assessed for inclusion: (1) the study should include the pulmonary rehabilitation and control group; (2) the outcome of the study should be one of the last items (postoperative complications, post-operative pulmonary complications, and mortality); (3) the study should include sufficient data for calculation. The exclusion criteria were as follows: (1) part of patients enrolled in the study not having received surgery.

If the same study cohort appeared in several articles, only the latest article was selected. Disagreements were resolved by discussion.

Data Extraction

Data were extracted from all selected studies by two reviewers who worked independently, using a standardized form to ensure that all relevant information was captured. The following data were extracted from each publication: author, publication year, country, study design, pre- or post-operation, number of each group, the pulmonary rehabilitation program, the frequency of pulmonary rehabilitation, the time of pulmonary rehabilitation, the choice of operation, tumor stage of the patients enrolled, post-pulmonary operation complications, postoperative pulmonary complications, and mortality. If data of the items mentioned above were not reported in the study, the item was treated as "not reported." Two reviewers assessed the Quality Rating Scheme for Studies (23). The third author assessed the data and resolved the disagreement.

Statistical Analysis

All calculations were carried out with Review Manger 5.1 statistical software. All the analysis was conducted according to the standard methods recommended for a meta-analysis of. For each study, we calculated the odds ratio (OR) with 95% confidence interval (CI) to summarize the effects of pulmonary rehabilitation programs on postoperative morbidity and mortality. The fixed or random regression model was applied, and $P < 0.05$ was regarded as statistically significant. I^2 statistics were used to detect statistically significant heterogeneity across the studies. Heterogeneity was evaluated by I^2: if $I^2 > 50\%$, an article was considered to display substantial heterogeneity, requiring subgroup analysis. The potential publication bias

was estimated by Deeks' funnel plots. A statistically significant publication bias existed if the *P*-value was <0.1 (24).

Begg's tests were used to detect any potential publication bias within the meta-analyses. The Begg's funnel plot showed the presence of bias visually.

RESULTS

Study Selection

Our search strategy identified 392 publications for consideration. Among these, 182 were irrelevant studies, and 85 reviews were removed. Then, the abstracts were reviewed: 81 studies were excluded because they did not report the three outcomes, 1 was written in French, and 1 was a case report. Of the 42 remaining publications, the full articles were obtained and reviewed, and another 29 studies were excluded for the following reasons: 20 studies were excluded because they enrolled advanced stage patients or not all patients received surgery, five studies were clinical trial protocol reports, two studies enrolled the same cohort, and two studies were not related to our study (**Figure 1**). Finally, 13 publications meeting all of the inclusion criteria were considered for the meta-analysis. Among them, five publications reported mortality, nine reported postoperative complications, and seven reported postoperative pulmonary complications.

Study Descriptions and Quality Assessment

The 13 publications enrolled 2,501 patients totally. Among them, eight studies were prospective designs, three were retrospective, and the remaining two did not report. Six studies reported surgery method (video-assisted thoracoscopic surgery (VATS) or open), seven reported the surgery type (wedge resection, sleeve resection, segmentectomy, lobectomy, bilobectomy, and pneumonectomy), and six studies reported the cancer stage. In seven studies, the pulmonary rehabilitation was conducted before surgery, in two studies it was conducted after surgery, and in the remaining four studies, it was performed both pre- and post-operation. All the 13 studies adopted at least one exercise training, six studies adopted physiotherapy, and three studies adopted bronchodilators or antibiotics. Besides, healthy education was added to five studies, and nutritional intervention was used in one study. Smoking cessation was emphasized in five studies. The details were showed in **Tables 1–3** and **Supplement Table 1**.

The data of quality assessment was showed in **Supplementary Figure 1**.

Mata-Analysis and Systemic Review

For postoperative complications analysis, nine studies enrolled 1,937 patients. The pooled OR was 0.62 (95% CI: 0.49–0.79), favoring the pulmonary rehabilitation. For subgroup analysis, we found the pre-surgery rehabilitation had a clinical significance, and the post- or pre-+post- only showed tendencies in favor of pulmonary rehabilitation.

For postoperative pulmonary complications analysis, seven studies enrolled 969 patients. The pooled OR was 0.39 (95% CI: 0.27–0.56) favoring the pulmonary rehabilitation. For subgroup analysis, we found the pre-surgery and pre-+post-surgery rehabilitation subgroups had a clinical significance, and the post-surgery subgroup only showed a tendency in favor of pulmonary rehabilitation.

For mortality analysis, five studies enrolled 1,598 patients. The pooled OR was 1.32 (95% CI: 0.54–3.23), no clinical significance was showed in rehabilitation group. For subgroup analysis, both the pre-surgery and pre-+post-surgery rehabilitation subgroups showed no difference in rehabilitation or control group.

The details were showed in **Figures 2A–C**.

All three analyses showed no publication bias. The $I^2 < 50\%$ and $P > 0.01$ in those three analyses. The funnel plot was showed in **Supplementary Figures 2–4**.

DISCUSSION

Surgery operation remains the optimal selection for early-stage lung cancer patients, and it was also a crucial part of a multidisciplinary team for advanced lung cancer patients. Lung cancer was related to smoking history, thus the patients always had chronic lung disease, heart disease, and cerebrovascular diseases at the same time (6, 36). Those risk factors may increase the PPCs after pulmonary operation (7). Besides, lung cancer patients suffered deconditioning, muscle weakness, fatigue, cachexia, and anxiety, those sufferings resulted in disability and impaired quality of life among lung cancer individuals (37, 38). Pulmonary rehabilitation was usually applied in chronic obstructive pulmonary disease, and it was significantly associated with a lower risk of death (39, 40). Pulmonary rehabilitation was also recommended for other chronic pulmonary diseases, interstitial lung disease, cystic fibrosis, lung cancer, etc. (10, 11). Several studies have supported the positive effects of rehabilitation in muscle strength, exercise endurance, well-being, and health status (25, 41–43), and it also relieved the discomfort from symptoms (44, 45). In recent years, pulmonary rehabilitation had been advocated by a wide range of surgical specialties, including cardiothoracic surgery. Many single-center-based studies have reported the clinical values of pulmonary rehabilitation. For those who would undergo pulmonary operations, the pulmonary rehabilitation program could apply before surgery, after surgery, or both pre- and post- surgery. For preoperative pulmonary rehabilitation, it can improve individuals' exercise tolerance and overall medical stability before surgery resection (46, 47). Those who received pulmonary rehabilitation after lung cancer resection surgery may gain increasements in walking endurance, peak exercise capacity, and decrease in dyspnea and fatigue (48, 49). At some centers, the pulmonary rehabilitation was applied during hospitalization (14, 28, 30).

Many studies had supported the positive roles of rehabilitation in decreasing postoperative complications and mortality, but the majority of them are based on a single center and a limited number of patients, and they thus could not avoid selection bias. The latest systemic analysis was published in 2019 and only enrolled publications before June 2017 (21). We therefore conducted this study to update the records and explore

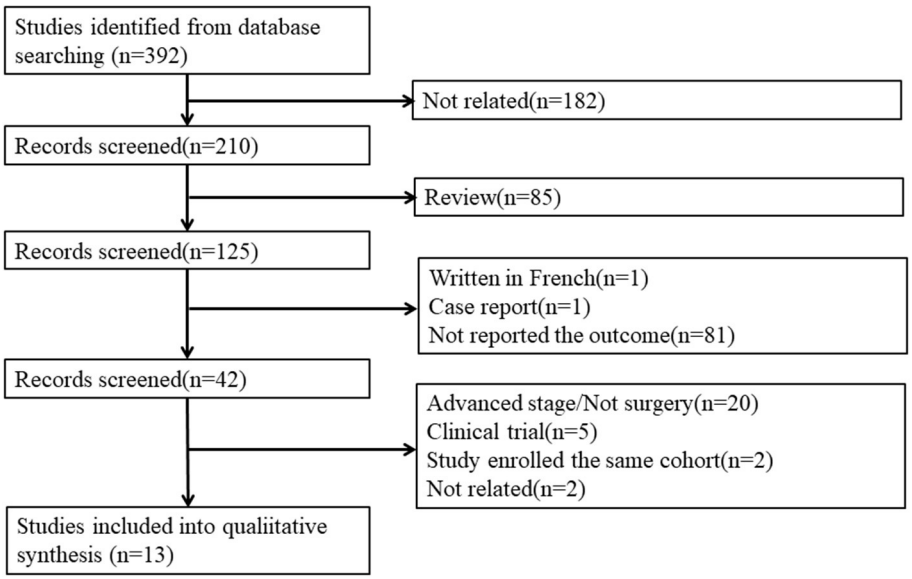

FIGURE 1 | The flow chart of the publication selection.

TABLE 1 | Baseline characteristics.

year	Author	Design	Group	Number	Sex (Male)	Age (Male)	Surgery method		Surgery type			Stage					References
							Open	VATS	WR/SR/ST	LB	BL/PN	I	II	III	IV	Unknown	
2011	Roberto Benzo	Prospective	Rehabilitation	9													(25)
			Control	8													
2011	Esra Pehlivan	Prospective	Rehabilitation	30		54.1			19	11	0						(26)
			Control	30		54.76			24	6	0						
2011	Gill Arbane	Unknown	Rehabilitation	26		65.4			26			15	6	2		3	(27)
			Control	25		62.6			25			10	6		5	4	
2013	Amy Bradley	Prospective	Rehabilitation	58	31	69											(28)
			Control	305	182	67											
2014	G. Arbane	Prospective	Rehabilitation	67	32	67	45	19				24	12	6	7	15	(29)
			Control	68	44	68	45	19				29	12	8	2	16	
2015	Ke Gao	Prospective	Rehabilitation	71	40	66.33	29	42				26	39	4	2		(13)
			Control	71	44	59.67	32	39				41	19	11	0		
2015	Oliwia Glogowska	Prospective	Rehabilitation	215	113	59*			61	7	147						(30)
			Control	187	102	55*			46	5	136						
2015	Natasa Mujovic	Unknown	Rehabilitation	56	49	62			43	13							(14)
			Control	47	41	59			42	5							
2016	Gemma CT	Prospective	Rehabilitation	33		64.5											(31)
			Control	9		75											
2016	Marc Licker	Prospective	Rehabilitation	74	41	64		12	49	13	12	33	28	13			(32)
			Control	77	50	64		14	46	17	14	40	27	10			
2017	Zhou Kun	Retrospective	Rehabilitation	197	116	58.5	75	122	197	0	0	102	69	24	2		(33)
			Control	742	406	58.8	253	489	742	0	0	350	303	81	8		
2017	Hajime Saito	Retrospective	Rehabilitation	31	27	72	20	11	31	0	0	18	8	5			(34)
			Control	31	27	71.3	18	13	31	0	0	20	6	5			
2018	Fairuz Boujibar	Retrospective	Rehabilitation	19	15	65	4	15									(35)
			Control	15	10	69	2	13									

*VATS, video-assisted thoracoscopic surgery; WR, wedge resection; SR, sleeve resection; ST, segmentectomy; LB, lobectomy; BL, bilobectomy; PN, pneumonectomy. *: median age.*

TABLE 2 | Pulmonary rehabilitation program of each study.

Year	Author	Pre/ post surgery	Time	Frequency	Physiotherapy			Bronchodilators/ antibiotic	Healthy education	Smoking cessation	Nutritional intervention
					Coughing exercise/ airway clearance	Inhalation therapy	Oxygen inhalation				
2011	Roberto Benzo	Pre		Total 10 sessions							
2011	Esra Pehlivan	Pre	1 w		√						
2011	Gill Arbane	Post			√						
2013	Amy Bradley	Pre+post			√	√	√		√	√	
2014	G. Arbane	Post									
2015	Ke Gao	Pre									
2015	Oliwia Glogowska	Pre+post			√				√		
2015	Natasa Mujovic	Pre+post	2–4 w	5/w	√	√		√			
2016	Gemma CT	Pre						√	√	√	
2016	Marc Licker	Pre								√	√
2017	Zhou Kun	Pre							√		
2017	Hajime Saito	Pre+post	2–4 w	5/w	√			√		√	
2018	Fairuz Boujibar	Pre	3–5 w						√	√	

Year	Author	Exercise training									References
		Upper arm training	Lower arm training (including walking, treadmill)	Abdominal respiration/ diaphragmatic breathing	Pursed lip	Segmental breathing/ deep breathing	Thoracic cage expansion	Other IMT	Cycle ergometry	Incentive spirometry	Exercise -not otherwise	
2011	Roberto Benzo	√	√					√		√		(25)
2011	Esra Pehlivan			√	√	√				√		(26)
2011	Gill Arbane										√	(27)
2013	Amy Bradley					√						(28)
2014	G. Arbane	√							√			(29)
2015	Ke Gao		√							√	√	(13)
2015	Oliwia Glogowska	√	√			√			√		√	(30)
2015	Natasa Mujovic			√			√				√	(14)
2016	Gemma CT		√					√	√			(31)
2016	Marc Licker		√						√		√	(32)
2017	Zhou Kun			√		√					√	(33)
2017	Hajime Saito			√			√	√	√		√	(34)
2018	Fairuz Boujibar	√	√								√	(35)

IMT, Inspiratory Muscle Training.

TABLE 3 | Postoperative outcomes.

Year	Author	Group	No. of patients	Mortality		PPCs		PPCs of lung		References
				No.	*p*	No.	*p*	No.	*p*	
2011	Roberto Benzo	Rehabilitation	9					3	0.23	(25)
		Control	8					5		
2011	Esra Pehlivan	Rehabilitation	30			1	0.04			(26)
		Control	30			5				
2011	Gill Arbane	Rehabilitation	26			2	NS			(27)
		Control	25			3				
2013	Amy Bradley	Rehabilitation	58	2	0.62			5	0.21	(28)
		Control	305	6				49		
2014	G. Arbane	Rehabilitation	67			20		10		(29)
		Control	68			22		16		
2015	Ke Gao	Rehabilitation	71			12	0	5	0.0004	(13)
		Control	71			59		25		
2015	Oliwia Glogowska	Rehabilitation	215			32	0.19			(30)
		Control	187			37				
2015	Natasa Mujovic	Rehabilitation	56	2	0.191	20	0.354	17	0.2	(14)
		Control	47	0		21		20		
2016	Gemma CT	Rehabilitation	33	0	0.05					(31)
		Control	9	1						
2016	Marc Licker	Rehabilitation	74	2	0.64	27	0.08	17	0.01	(32)
		Control	77	2		39		33		
2017	Zhou Kun	Rehabilitation	197	2	0.611	36	0.022			(33, 36)
		Control	742	4		194				
2017	Hajime Saito	Rehabilitation	31			2		2		(34)
		Control	31			5		5		
2018	Fairuz Boujibar	Rehabilitation	19			8	0.038			(35)
		Control	15			12				

PPCs, post-pulmonary operation complications.

the clinical value of pulmonary rehabilitation in decreasing postoperative complications and mortality.

After selection, nine studies enrolled 1,937 patients in total and reported postoperative complications, and seven studies enrolled 969 patients in total and reported pulmonary complications. In our study, pulmonary rehabilitation had proved the clinical values in decreasing the postoperative complications for patients, especially pulmonary complications. Previous research suggested that pulmonary function was a good predictor for pulmonary resection, including, for example, the forced expiratory volume in one second (FEV1), forced vital capacity (FVC), carbon monoxide diffusing capacity (DLCO), the cardiopulmonary exercise test (CPET), impulse oscillometry (IOS), etc. (50–54). Pulmonary rehabilitation has been proven to improve the cardiopulmonary function, exercise tolerance, anxiety, depression, etc. (46, 55–61). Lai et al. suggested that pre-surgery pulmonary rehabilitation may improve the FEV1, FVC, and 6-minute walking test (6MWT) (58, 59). Jones's study, apart from pulmonary function, observed an improvement in cardiopulmonary function after presurgical exercise training (46). Stefanelli et al. measured using the BROG scale and found the modified breath in chronic obstructive pulmonary disease (COPD) patients after high-intensity training and cardiopulmonary exercise. In Cavalheri's study, post-surgery pulmonary rehabilitation showed positive values in pulmonary function, cardiopulmonary function, and mental fitness (57). Vagvolgyi's study also demonstrated the clinical value of post-surgery pulmonary rehabilitation (60). Besides, pulmonary rehabilitation may decrease the level of cytokine and inflammation factors. In Messaggi-Sartor's study, after an 8-week training program, an increase of 0.61 μg/mL in the serum IGFBP-3 levels for patients in the intervention group was observed (61). Fiorelli et al. reported a lower level of Serum IL-6 ($P = 0.001$), IL-10 ($P = 0.001$), and TNF-α ($P = 0.001$) in the transcutaneous electrical nerve stimulation group than in the control group (55). In our analyses, we showed a positive result of pulmonary rehabilitation, especially in the pre-surgery subgroup. This may be because the outcome of this study was the main complications after surgery. Pre-surgery rehabilitation improved pulmonary function and cardiopulmonary function before an operation, thus decreasing complications after surgery. For the post-operation rehabilitation subgroup, it showed a favoring of the pulmonary rehabilitation group, but the result was not statistically significant. We inferred that the complications occurred before the pulmonary rehabilitation worked. We suggested the pre-surgery pulmonary rehabilitation should be

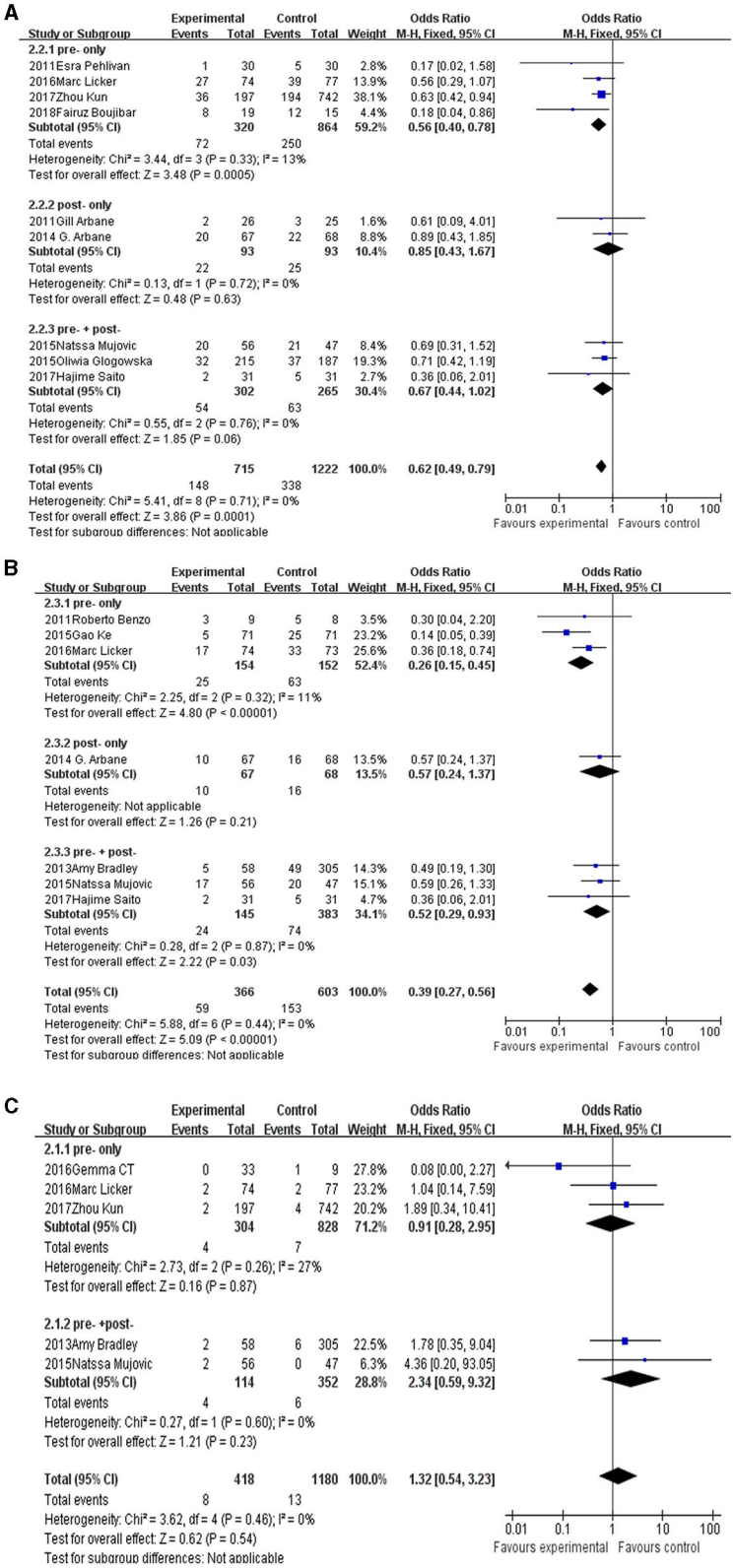

FIGURE 2 | The forest plot of postoperative complications **(A)**, postoperative pulmonary complications **(B)**, and mortality **(C)**.

operated as perioperative interventions, especially for high-risk patients. The main goal of perioperative rehabilitation is to improve pulmonary function, avoiding atelectasia, pneumonia, etc. Herin, apart from calculating the pooled effect of the postoperative complications, we specifically calculated the pooled OR of decreasing postoperative pulmonary complications. We found the pulmonary rehabilitation worked better in decreased PPCs than total complications. This may be because the rehabilitation program focuses on the lung.

Some studies have argued for the positive clinical value of pulmonary rehabilitation in long-term survival for those pulmonary resection patients (61, 62). While perioperative rehabilitation would improve lung function, other organs would gain beneficence from this procedure, such as the heart. Mortality related to heart disease and related issues would decrease. But in this study, the pulmonary rehabilitation did not show the clinical value for mortality in those who received pulmonary surgery in either the pre-operative group or pre-+post- group. As mentioned above, pulmonary rehabilitation could improve cardiopulmonary function, exercise tolerance, etc. Those factors also were effective predicted factors for mortality, such as DLCO (63, 64). Both pre- and post-surgery pulmonary rehabilitation showed an improvement in DLCO (56, 65). In our study, no significant value of pulmonary rehabilitation in reducing mortality was observed, several reasons may account for the result. Firstly, only five studies were enrolled in this meta-analysis, limited people were enrolled, especially the rehabilitation group. Secondly, it could be attributed to the development of surgical techniques. Among them, two studies reported on surgical methods. In Licker's study, all patients received VATS. In Zhou's study, more than half of the patients performed VATS. This means low mortality would be observed in those cohorts. Thirdly, some studies were not RCT, so select bias could not be avoided.

Our study also had some limits. Firstly, for defined outcomes, only a few studies were included in the meta-analysis. This may result in publication bias. Secondly, some studies were not randomized controlled trials, and this may cause selected bias when conducted the clinical trial. Thirdly, the studies enrolled were mostly performed in one center, which also resulted in select bias. Forth, it is difficult to divide complications directly related to surgery from those related to comorbidity, and we summarize the complications as PPCs and total complications.

Summarily, pulmonary rehabilitation is meaningful in avoiding postoperative complications of pulmonary resection. We suggested that pulmonary rehabilitation should be included in the perioperative period, and perioperative pulmonary rehabilitation was the most important part of the program. Also, a more well-designed RCT is required to provide proof of our results.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

XM, YNi, and YNiu conducted the literature search and data extraction. XM wrote the manuscript. YNi revised the manuscript. LJ reviewed the manuscript and directed and supervised the study. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.685485/full#supplementary-material

Supplement Table 1 | Main pulmonary rehabilitation protocols.

Supplementary Figure 1 | Quality rating scheme for enrolled studies.

Supplementary Figure 2 | Funnel plot of postoperative complications.

Supplementary Figure 3 | Funnel plot of postoperative pulmonary complications.

Supplementary Figure 4 | Funnel plot of mortality.

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