The role of prehabilitation in improving peri-operative outcomes in elective colorectal and hepatobiliary cancer surgery

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This thesis is dedicated to my family and wide friendship network that have provided me with the impetus, support and encouragement to take steps when my legs could no longer carry me. To my mentor, brother and friend Mr Daren Subar, I will always be grateful for the opportunity to share ideas and work with you. Hopefully we can work collaboratively in the future to improve the outcomes of our patients. To my supervisory Team, Dr Chris Gaffney, Dr Tom Keegan and Mr Daren Subar, without your guidance and expertise this body of work may have been confined to a small part of our collective consciousness. Thank you all.

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If I cannot do great things, I can do small things in a great way

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Declaration

This thesis has not been submitted in support of an application for another degree at this or any other university. It is the result of my own work and includes nothing that is the outcome of work done in collaboration except where specifically indicated. Many of the ideas in this thesis were the product of discussions with my supervisors, Dr Chris Gaffney , Dr Tom Keegan and Mr Daren Subar and other academic and healthcare professionals.

Excerpts of this thesis have been published in the following conference manuscripts and academic publications. A shortened version of Chapter 1 has been published in the Annals of Surgery (Publication item **1.** Below). Publication item **3.** Is under review and is an adapted version of Chapter 2.

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Publications

Published Papers

1. The Impact of Prehabilitation on Patient Outcomes in Hepatobiliary, Colorectal, and Upper Gastrointestinal Cancer Surgery: A PRISMA-Accordant Meta-analysis. Ann Surg. 2021 Jul 1;274(1):70-77. doi: 10.1097/SLA.0000000000004527. PMID: 33201129. Lambert JE, Hayes LD, Keegan TJ, Subar DA, Gaffney CJ.

2. The Effect of the Enhanced Recovery Programme for Liver Surgery on Long Term Survival. Langenbeck's Archives of Surgery volume 408, Article number: 239 (2023). Joel Lambert, Kalaiyarasi Arujunan, Thomas Mair, Abdul Shugaba, Harmony Uwadiae, Anne Livesey, Georgios Sgourakis, Chris Gaffney, Daren Subar.

3. A comparative analysis of cardiopulmonary exercise testing variables predictive of survival in major colorectal & hepatopancreatobiliary cancer surgery. Joel Lambert Anton Krige Kerry Foley Thomas Keegan, Rebecca Killick, Daren Subar, Chris Gaffney.(Currently under review pending publication).

Letters to the Editor

4. Response to the Comment on “The Impact of Prehabilitation on Patient Outcomes in Hepatobiliary, Colorectal and Upper Gastrointestinal Cancer Surgery: A PRISMA-Accordant Meta-analysis”. Annals of Surgery 274(6):p e932-e933, December 2021. | DOI: 10.1097/SLA.0000000000005083. Lambert Joel, Hayes Lawrence, Keegan Thomas, Subar Daren, Gaffney Christopher.

5. Response to the Comment on “Prehabilitation in Major Abdominal Surgery”. Annals of Surgery 274(6):p e944-e945, December 2021. DOI:

10.1097/SLA.0000000000005224. Lambert, Joel, Hayes, Lawrence, Keegan Thomas PhD; Subar, Daren, Gaffney, Christopher.

6. Response to the Comment on “The Impact of Prehabilitation on Patient Outcomes in Hepatobiliary, Colorectal, and Upper Gastro-intestinal Cancer Surgery: A PRISMA-Accordant Meta-analysis”. Annals of Surgery 274(6):p e946-e947, December 2021. | DOI: 10.1097/SLA.0000000000005223. Lambert Joel, Hayes Lawrence, Keegan Thomas, Subar Daren, Gaffney Christopher.

Book Chapter

7. Prehabilitation for Gastrointestinal Surgery. Recent Strategies in High Risk Surgery. Joel Faintuch & Salomao Faintuch(Eds). In press.

Oral Presentations

8. Prehabilitation in Cancer Surgery. Sunway Conference December 2020.
9. Exercise & Cancer Surgery. Advanced Physiology Lecture Series. Lancaster University 2021.
10. The SPECS Clinical Trial. Blackburn Research Innovation & Development Group in Surgery. Quarterly Review 2021-2023.
11. Prehabilitation in Surgery Workshop. Lancaster University March 2023.
12. The SPECS Trial Results. MASILASC Regional Conference. Bolton October 2023.
13. Prehabilitation prior to major cancer surgery. Baxter Hepatopancreatobiliary Training Day. Birmingham January 2023

Abstract

Introduction (chapter 1): This thesis constitutes two studies and a systematic review & meta-analysis. All three have involved different methodologies and two out of the three have been designed to investigate the relationship between prehabilitation and clinical outcomes

Methods (chapter 2) Data chapter: This retrospective analysis involved interrogation of a prospectively maintained single-site cardiopulmonary exercise testing (CPET) database to determine what CPET and oncological factors were associated with complications and survival.

Methods (chapter 3) The SPECS Trial: This was a randomised-controlled trial comparing standard care with prehabilitation in patients undergoing elective major hepatobiliary (HB) and colorectal cancer resections. Patients were randomised 1:1 to either standard care or prehabilitation. Blood biochemistry, circulatory cytokines, CPET, body composition and handgrip strength(HGS) were measured at baseline, preoperatively and postoperatively to determine biological and physiological responses to an exercise-based prehabilitation programme.

Results (chapter 1): Prehabilitation led to a statistically significant reduction in length of hospital stay (LoS) by 2 days. There were no difference in complication rates or mortality.

Results (chapter 2): In colorectal cancer patients, a R0 resection margin was associated with improved survival (HR: 0.392 CI 0.167 – 0.998 p=0.038) while

female sex conferred significantly better survival (HR 0.464 CI 0.215 – 0.930 p=0.038) compared with males. An increasing number of CRI factors was associated with significantly poorer survival (HR 1.746 CI 1.163 – 2.573 p=0.005). A high VE/VCO_2 was associated with a trend towards reduced survival (HR:1.870 CI 0.920 – 3.659 p=0.073). In colorectal liver metastases(CRLM), the main determinants of survival were R0 resection margin (HR 0.341 CI 1.153 – 7.144 p=0.019) and total number of metastasectomies (HR 0.639 CI 0.485 – 0.956 p=0.032).

Results(chapter 4): Prehabilitation was associated with a potential cardiovascular protective effect evidenced by reduced PAI-1 and leptin levels. There was a statistically significant improvement in anaerobic threshold (AT) noted in the prehabilitation group compared to standard in the postoperative period. Prehabilitation did not demonstrate improvements in LoS, complication rates or mortality.

Conclusions: A moderate intensity exercise-based prehabilitation programme can improve cardiovascular fitness by promoting biological and physiological adaptation in the short to medium term.

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List of Abbreviations and Acronyms

6MWT: 6-Minute Walking Test

AC: Adjuvant Chemotherapy

ANOVA: Analysis of Variance

APR: Abdominoperineal resection

ARISCAT: Assess Pulmonary Risk in Surgical Patients in Catalonia

ASA-PS: American Association of Anaesthesiologists Performance Score

AT: Anaerobic Threshold

BMI: Body Mass Index

CD: Calvien-Dindo

CI: Chief Investigator

COI: Co-Investigator

CONSORT: Consolidated Standards of Reporting Trials

CPET: Cardiopulmonary Exercise Testing

CRI: Cardiac Risk Index

CRM: Circumferential Resection Margin

CRLM: Colorectal Liver Metastases

CT: Computed Tomography

DXA: Dual-energy X-ray Absorptiometry

ERP: Enhanced Recovery Programme

ESPEN: European Society for Clinical Nutrition and Metabolism

FBC: Full Blood Count

FC: Functional Capacity

FLR: Future Liver Remnant

GI: Gastrointestinal

GLP-1: glucagon-like peptide-1

GP: General Practitioner

HGS: Hand Grip Strength

HiiT: High intensity interval training

HPB: Hepatopancreatobiliary

HB: Hepatobiliary

HCC: hepatocellular carcinoma

HR: Hazard Ratio

HRA: Health Research Authority

HVE: hepatic vein embolisation

ICU: Intensive Care Unit

IQR: Interquartile Range

IPQ: Illness Perception Questionnaire

ISGLS: International Study Group on Liver Surgery

IL-1β: Interleukin 1 beta

IL-6: Interleukin 6

IMT: Inspiratory Muscle Training

LiRad: Liver image reporting & data systems

LoS: Length of Hospital Stay

MACS: Mental Adjustment to Cancer Scale

MCID: Minimal Clinical Important Difference

MDT: Multidisciplinary Team

MI: Minimally Invasive

NAC: Neoadjuvant chemotherapy

NAT: Neoadjuvant Therapy

NHS: National Health Service

NF κB: Nuclear Factor κB

PAI-1: plasminogen activator inhibitor-1,

PEDro: The Physiotherapy Evidence Database

PG-SGA: patient generated subjective global assessment tool

POETTS: Peri-operative Exercise Testing & Training Society

POC: Post-operative complications

PPI: Patient Public Involvement

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PVE: Portal Vein Embolisation

P value: probability value

RCT: randomised controlled trial

REC: Research Ethics Committee

RER: Respiratory Exchange Rate

RFA: Radio Frequency Ablation

ROS: Reactive Oxygen Species

R0/R1: Resection Margin Status

RR: readmission rates

SABR: Stereotactic Ablative Body Radiotherapy

SEM: Standard Error of the Mean

SD: Standard Deviation

SPECS: Standard Care vs Prehabilitation in Elective Colorectal & HPB Surgery

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trial

TGF: Transforming Growth

TNF-α: Tumor Necrosis Factor Alpha

TNM: Tumour Node Metastasis

UCT: Uncontrolled trial

VE/VCO_2: Ventilatory Equivalent for CO_2

VO_2 peak: Peak Oxygen Uptake

VO_2 max: Maximal oxygen Uptake

QoL: Quality of Life

Contents

Chapter 1: Introduction & Background

1.1 Introduction

The modern delivery of surgical care has had to innovate in step with advances in newer radiological, surgical and oncological techniques. Prehabilitation as a strategy to improve postoperative outcomes has shown promise as an important adjunct within pre-existing well establish surgical care pathways such as enhanced recovery.

There is conflicting published data on the effectiveness of prehabilitation as a preoperative intervention[1–6]. At the core of this apparent conflict is that prehabilitation may come in several different forms and when employed in biologically and physiologically different patient groups either show no difference or marginal benefit. This could suggest that prehabilitation may have to be tailored based on the patient population, type of cancer, and what is practically feasible based on finite resources. This thesis seeks to answer questions on the efficacy of prehabilitation and further to investigate the biological and physiological responses to prehabilitation in colorectal cancer and colorectal liver metastases.

1.2 Defining prehabilitation & the case for its use in cancer surgery

The term ‘prehabilitation’ has gained popularity over the last few years as a series of interventional strategies such as exercise, nutrition and psychosocial support aimed at improving patients’ physical fitness and mental well-being prior to surgery[5].

Prehabilitation strategies may encompass one of these modalities (unimodal prehabilitation)[7,8] or two or more (multimodal prehabilitation)[3,9]. Improving clinical outcomes after cancer surgery has been the focus of several National

Health Service (NHS) initiatives over the years. This has led to a greater emphasis on improving the cardiorespiratory fitness of patients for major cancer surgery[10]. In practice, the implementation of prehabilitation programmes has been integrated into other well-established practices such as the enhanced recovery after surgery (ERAS) programmes [11]. Whereas ERAS focuses on interventions to speed up recovery from surgery, prehabilitation emphasises improved fitness prior to surgery.

It is currently unclear from the published literature which components of prehabilitation have the largest impact on patient outcomes[3,12]. There is also debate over the duration of prehabilitation programmes and the minimum compliance and engagement levels required to realise measurable clinical benefits[13,14]. Ultimately, the goal of prehabilitation is to give patients the best opportunity to recover from cancer surgery and to improve their peri-operative outcomes. These may include reduced hospital length of stay, reduced incidence of complications, improved functional capacity, reduced morbidity and mortality, and a greater sense of wellbeing.

National Health Service (NHS) targets for diagnosis and treatment of cancers mean that the time available for prehabilitation is often dictated by the period between diagnosis and curative surgical treatment[15]. For some cancers, for example rectal, patients often undergo neoadjuvant chemo-radiotherapy for 8-12 weeks before surgical intervention. Feasibly, this time could be spent engaged in a prehabilitation programme which would give the patients the opportunity to improve their cardiovascular fitness. For other cancers, such as fast track resectable pancreatic cancers, the time from diagnosis to surgery is often a few weeks[16]. These time limits challenge the practical application and subsequent efficacy of any prehabilitation programme as studies have shown a minimum of 4 weeks[7] high intensity exercise and up to 6 weeks[9] may be required to improve cardiovascular fitness.

The ethos of prehabilitation operates on the premise that patients with superior cardiorespiratory fitness have better post-operative outcomes. Specifically

these outcomes might include improved functional capacity[17], reduced post-operative complications[17,18] and reduced length of hospital stay (LoS)[9,18,19], thereby increasing the likelihood of completing adjuvant chemotherapy if required. However, it is accepted that improved fitness through prehabilitation does not necessarily confer a guarantee of reduced complications or improved survival[20]. It is likely that less fit patients are more likely to benefit from prehabilitation as there is the opportunity to improve cardiovascular and respiratory physiology from a lower baseline fitness level[21]. What is yet unknown is whether certain cancer patients are more or less likely to respond to prehabilitation and how can we identify these potential subgroups to better target prehabilitation interventions. A starting point in answering this question may be centred around better understanding of the molecular and mechanistic processes that underpin prehabilitation. This thesis will examine the efficacy of prehabilitation in the context of elective cancer surgery for colorectal and colorectal liver metastases.

1.3 Components of Prehabilitation

Prehabilitation components may be single or multiple coined 'uni-modal' or 'multimodal'. There exists wide variations in the types, duration and volumes of exercise. Likewise various nutrition regimens exist and are often designed to have a complementary effect alongside exercise. There is a paucity of evidence for psychosocial interventions within the published literature. In general these strategies are aimed at empowering patients by introducing coping mechanisms and improving mental resilience to illness. This may reflect a disproportionate focus on physical measurable outcomes that are easier evaluate economically.

1.3.1 Exercise

Of the three components of prehabilitation, exercise has been the mostly widely studied[3,4,7,9,20]. Several studies have investigated the impact of exercise on improving overall cardiovascular fitness before surgery[7,22]. Physiological improvements in cardiovascular fitness have been measured using

cardiopulmonary exercise testing (CPET) variables such as the maximum oxygen consumption at the anaerobic threshold ($\dot{V}O_2$ AT) and oxygen consumption at peak aerobic exercise ($\dot{V}O_2$ max)[7,23,24]. Deficiencies in these two measures along with reduced ventilatory efficiency for carbon dioxide are associated with poorer post-operative outcomes[25]. It is accepted that the minimal clinically important difference (MCID) would be a pre-operative increase in $\dot{V}O_2$ AT of 1.5-2.0 ml/kg/min[7,24]. These physiological improvements may have important clinical implications as patients may be turned down for potentially curative surgery due to low levels of fitness implying a higher risk of complications and mortality. Improving these parameters may move patients from high to moderate or moderate to low risk thereby dictating eligibility for major surgery.

Exercise interventions may vary in type (aerobic/strength training), duration, intensity (low, moderate, high) and frequency. These exercise variables have a bearing on the level of cardiovascular stress induced. Exercise may combine aerobic and strength training and the intensity of such a regime may be measured by the fraction of $\dot{V}O_2$ peak attained. For example low intensity training; 44-51%, moderate intensity 52-67% and high intensity >92%[26]. Within the context of prehabilitation, studies reported significant variation in how these exercises were performed in terms of types, duration and volume. For example, some programmes involved concurrent aerobic/strengthening exercise programmes[18,27] alternatively patients were enrolled into a bespoke training regime such as high-intensity interval training (HIIT)[7]. Exercise has been shown to improve CPET variables ($\dot{V}O_2$ AT, $\dot{V}O_2$ peak) and functional capacity pre-operatively and this improved fitness is sometimes sustained beyond the operative period[7,28]. Although it is unclear as to the influence of exercise on complication rates, there is general consensus that if patients are able to increase their oxygen carrying capacity and improve muscle quality and function that this may lead to reduced respiratory and operation-specific complications[21].

It has been shown that unsupervised exercise programmes , regardless of type, intensity, duration or frequency suffer from poor participant compliance and adherence[29]. Studies have suggested that psychobiological factors such as motivation, percentage body fat and weight discriminated 'adherers' from 'drop-outs' in 80% of a 66 male participant study population[30]. Other studies have suggested that a lack of time may be the most important factor in poor adherence rates[31].These factors may also be important in cancer cohorts. However, the psychosocial and physiological impact of a cancer diagnosis, concurrent cancer treatment and how this might influence exercise adherence remains to be elucidated.

There is also evidence to suggest that studies involving moderate to high intensity exercise programmes are challenged by low adherence rates[12,32]. It is reasonable to theorise that patients who have low levels of baseline fitness may be more likely to drop-out because of unfamiliarity with exercise programmes, a lack of motivation and early exhaustion. These observations may also be a reflection on the physiological limitations within these patient populations combined with the effects of other concurrent cancer treatments such as radio/chemotherapy which may affect baseline fitness. In fact, one study found that increased adherence positively correlated with higher levels of baseline fitness. In a cohort of oesophagogastric cancer patients a >75% adherence was associated with a higher baseline $\dot{V}O_2$peak[32]. While supervised exercise programmes have been shown to offer better compliance, within the context of the global Sars-2 Covid-19 pandemic, face/face supervised exercise programmes have been challenged due to government restrictions and raises other patient safety concerns such as difficulties with travel and the risk of virus transmission. The design of innovative and effective exercise training strategies within this context will be important in the coming years, specifically cognisant that most of these patients may be shielded due to concurrent cancer treatments.

1.3.2 Nutrition

The idea of nutritional optimisation before gastrointestinal (GI) cancer surgery may be rooted in the observation that digestive tract cancer sufferers tend to be mal/undernourished at the time of presentation[33]. Evidence from these populations suggests that calorie intake is reduced, immediately putting patients in a catabolic ("breakdown") state and this is in addition to the "wasting" effect of some solid tumours known as cancer cachexia[34]. This process is thought to be mediated via various cytokine pathways[35]. Additionally, the majority of cancer patients present between the 6th to 8th decades, where there is a higher prevalence of age-related sarcopaenia manifest through impaired muscle signalling pathways[35].

Several prehabilitation studies have advised nutritional supplementation to be taken prior to an exercise training regime[12,18,36]. This is to "correct" nutritional deficiencies to allow the exercise component to take full effect. In fact, some studies have suggested vitamin D as crucial in building and maintaining skeletal muscle health[37,38]. The nutrition component often involves carbohydrate, fat and protein supplementation to be taken alongside patients' normal caloric intake[5,17]. In specific cases where there is pancreatic exocrine and endocrine insufficiency such as in pancreatic cancer, pancreatic enzyme replacement therapy may be administered alongside other protein and carbohydrate supplementation[4,19].

The literature on the use of nutrition as a standalone intervention within prehabilitation programme is sparse. One study using whey protein as a single intervention versus placebo suggested clinically significant improvements in functional capacity, measured by their ability to walk a further distance in a set timeframe[8]. It may be intuitive to suggest that the interaction between optimised nutrition and exercise may produce clinically relevant improvements. However, the physiological mechanisms underpinning this within cancer cohorts is poorly understood. Due to the wide variability and inherent logistic difficulties in assessing caloric intake it is yet unknown what the optimal proportions of

carbohydrate, fat, protein and micronutrients (vitamins and minerals) that are necessary to see meaningful improvements in outcomes.

Prehabiitation programmes involving nutrition attempt to assess patients' nutritional states at baseline with the objective of making patients eucaloric and supplementing beyond that[8,17]. Both these studies employed the patient generated subjective global assessment tool (PG-SGA) tool to establish baseline nutritional state. Caloric deficit was calculated from analysing these scores and from patient food diaries. This information was then used to design individualised nutrition supplemental regimes based on European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines[39]. The challenge in collecting and analysing such data lies in the wide variability in the accuracy of self-reporting of caloric intake. Additionally there is the issue of variability in compliance to supplemental nutrition which may reduce the validity or invalidate any observed differences in outcomes. While some studies investigating nutrition-based prehabilitation reported good compliance[8,17] even as high as 100%[3] others reported as low as 43%[12]. The challenge for prehabilitation programmes with nutrition as a component would be a design that is able to help patients accurately record their caloric intake while improving compliance and adherence to supplementation.

1.3.3 Psychosocial support

A cancer diagnosis with the perceived demands of treatment, a loss of control and the impact on carers and family can be psychologically demanding. Cancer care strategies have evolved over time to reflect a more holistic and patient-centred approach[40]. In practice this may involve bidirectional flow of information between the cancer care team and the patient to gauge immediate and medium-term needs. Several studies have suggested that supporting and addressing patients' psychosocial needs may have an impact on compliance to treatment, overall wellbeing and survival[41,42]. Several prehabilitation studies that have made use of psychosocial therapies have focused on stress and anxiety reduction techniques[3,22,43]. While it is unclear from the literature as to the role

of particular psychosocial interventions in influencing outcomes, it is accepted that improving the mental wellbeing of patients pre-operatively may have benefits.

1.4 Potential Benefits of Prehabilitation

There is conflicting published evidence on the benefits of prehabilitation. This may not be an unusual observation given the diverse patient groups and prehabilitation interventions currently being reported on. Generally outcomes measures detailed in most studies include time to recovery, complication rates, mortality and well-being. Objective measurements of changes in levels of fitness has gained further traction through the work of authors aiming to determine whether exercise can increase aerobic capacity prior to surgery.

Within this thesis, the SPECS Trial chapter will focus on objective physiological and biological measurements such as body composition, CPET outcomes and cytokine profiles, respectively, to assess of these corelate with the clinical outcomes mentioned below.

1.4.1 Reduced length of hospital stay

Several studies have assessed the impact of prehabilitation on length of hospital stay[9,43,44]. ERAS has demonstrated reduced complication rates and accelerated recovery and has been the established standard of care in most UK cancer units[45]. It is thought that prehabilitation may provide further gains by better preparation prior to surgery. Length of stay is often linked to post-operative complications, but may also be confounded by other social and non-medical factors such as community/social support provisions, medicines reconciliation issues and factors related to occupational therapy.

1.4.2 Improved functional capacity

The physical impact of surgery can often impair patients' abilities to perform various physical activities post-operatively. Functional capacity attempts to

quantify the extent to which patients recovering from surgery can perform basic functional activities[46]. The six-minute walk test (6MWT) has been validated for use within this context[47].

However, there is conflicting evidence on whether prehabilitation has any meaningful effect on functional capacity. While several studies have shown improvements[5,17,22] others have shown no benefit[8,44]. There may be several reasons to account for this including the magnitude of changes that are deemed significant by different authors, the different modalities of prehabilitation being used, the sensitivity of the method of fitness assessment (e.g. CPET vs. 6MWT), and vast differences in cancer patient cohorts.

1.4.3 Impact on morbidity & mortality

Elective cancer surgery mortality rates are often reported at 30, 60 or 90 days. This period covers the time in hospital and first outpatient follow-up sessions. However, more meaningful measurements are medium and long-term disease-free and overall survival measured in years. To date, there are no large prehabilitation studies that have looked at long-term disease free and overall survival.

Morbidity in the peri-operative period is associated with complications. Complications may be operation specific such as delayed gastric emptying in pancreaticoduodenectomies or generic as in respiratory or cardiovascular complications. Clavien-Dindo have suggested a framework for the classification of complications hinged on the type of intervention necessary to remedy the complication[48]. Grades I-IV have been extensively studies and quoted in the literature with moderate and severe complications classed as III & IV respectively.

1.4.4 Improved well-being

The effects of exercise on wellbeing in different contexts such as on mental health in non-cancer populations have been well studied[49,50]. Mandolesi et al,

argue that this improvement may be brought about by exercise-induced structural and functional changes in the brain[50]. Dunne et al assessed wellbeing after high intensity exercise prehabilitation by analysing a range of psychosocial parameters including mental health, social functioning and vitality. Their randomised controlled trial concluded that prehabilitation improved wellbeing and overall quality of life measures[7].

Within the prehabilitation literature and cancer surgery, there are very few studies that have assessed the impact of psychosocial interventions as standalone measures. This may be due to the fact that the evidence base for prehabilitation is still developing. It is also plausible that studies have been focusing on assessing outcomes that may be more tangible and measurable. It is likely that exercise may play a role in stress reduction and wellbeing[51,52], however, the data measuring the magnitude of this effect within the context of prehabilitation programmes is lacking.

1.5 Measurement of Outcomes

1.5.1 Functional capacity

Several studies have employed the six-minute walking test (6MWT) as a measure of functional capacity[8,22,27] However, as a practical measure, functional capacity encompasses much more than a patient's ability to walk a particular distance in six minutes.

It may also involve the ability to complete basic and more complex tasks of daily living, some which, such as cooking, cleaning and self-care, may require cognitive and motivational engagement. Across studies there is considerable variation as to what extent of change in 6MWT can be deemed as clinically significant. Within a clinical context a reasonable change in functional capacity might mean how quickly a post-operative patient can perform basic activities of daily living such as getting out of bed and self-care. This may be important as it is often a criterion for discharge from hospital. If prehabilitation improves

functional capacity, patients may more quickly get back to their baseline fitness after a surgery and have shorter hospital stays.

1.5.2 Cardiopulmonary exercise testing (CPET)

CPET measures the performance of the cardiovascular and respiratory systems, assesses the way the body consumes oxygen and expels carbon dioxide at rest and during exercise. It uses various directly measured and derived physiological parameters to compute an individualised score representative of the overall fitness of patients (**table 1.0**). This quantifiable measure is also linked to an estimated risk of peri-operative mortality and morbidity. CPET-derived values such as anaerobic threshold (AT) and peak oxygen consumption ($\dot{V}O_2$ max) can be objectively measured. Exercise programmes have been shown to improve patients' surgical risk profiles by increasing parameters such as $\dot{V}O_2$ max and oxygen consumption at anaerobic threshold.[7]

A CPET test is administered by asking patients to perform graded aerobic exercise on a cycle ergometer or treadmill, although the latter is rarer in clinical settings. The duration of exercise is usually 8-12 mins with a starting period of unloaded exercise and a recovery period at the end[53]. Dynamic measurements include blood pressure, gaseous exchange, heart rate, electrocardiogram analysis and oxygen saturation. Measurement of these values are integrated and expressed in graphical form from which other values (AT and $\dot{V}O_2$ max can be derived. These indices are important as they have been shown to correlate strongly with outcomes after cancer surgery[23,24]

Table 1.0 Description of CPET variables

(adapted from Peri-operative Exercise Testing & Training Society- POETTS) 2020 course handbook https://ebpom.org/poetts-cpet-course/ accessed 06/02/2024

Term (units of measurement)	Name	Description	Normal Values							Explanation/abnormalities
V̇O2 max (ml/kg/min)	Maximum oxygen consumption	The amount of oxygen consumed at maximal exercise	Age	20-29	30-39	40-49	50-59	60-69	>70	<15ml/kg/min associated with increased peri-operative risk <10ml/kg/min very high peri-operative risk
			M	40	31	28	26	22	21	
			F	31	22	20	18	16.6	16	
AT (ml/kg/min)	Anaerobic threshold	The point on the test where energy from anaerobic production starts supplementing aerobic energy	15.25 ml/kg/min 40-80% V̇O2max							<9-10 associated with increased peri-operative risk
V̇O2/WR (ml/min/Watt)	Oxygen consumed due to work load	Measures the efficiency of work	10 ml/kg/watt Range of 9-12							Values <9 indicate inefficient work any may suggest cardiac abnormalities

Peak oxygen pulse (ml/beat)	Peak oxygen pulse	The maximum volume of oxygen consumed per heart beat	> 80 % predicted. For males 15-20. For females 10-15	This value is reduced in deconditioning and heart failure
VE/VCO_2 at AT or minimum $VECO_2$	Ventilatory equivalent for carbon dioxide	Measures efficiently of expelling carbon dioxide at the anaerobic threshold	23-34 and increased with age to a maximum of 32	>34 is associated with increased peri-operative risk attributable to heart failure and/or lung disease
RR(breaths/min)	Respiratory Rate	Represents the rate of breathing	8-12	
Rest RER	Resting respiratory exchange ratio	Denotes exchange ratio between oxygen and carbon dioxide at normal breathing	0.7-1.0	>1 suggestive of hyperventilation
Peak RER	Peak respiratory exchange ratio		>1.15	Suggests maximal physiological effort

1.6 Challenges in measuring outcomes

One of the main challenges in assessing the pooled effect of outcomes (functional capacity, complication rates, length of hospital stay and mortality) has been the lack of standardisation amongst prehabilitation studies. An analysis of prehabilitation exercise regimes across the literature has revealed wide variations in intensity (mild, moderate, high), type (strength versus aerobic), duration and frequency of exercise. Additionally the definitions of exercise intensity can be ambiguous and readers may have to assume categorisation based on other parameters such as heart rate and exertional values. While sub-group analyses provide an opportunity to group these categories together, sample sizes are often too small to accommodate this.

A particular issue when measuring functional capacity by using 6MWT is the improvement in walking distance that is deemed clinically important. This value varies amongst studies. Statistically significant improvements in walking distances may not translate to clinically relevant improvements in functional capacity for reasons already stated.

Ultimately, any improvement in outcomes may depend heavily on patients' compliance, overall motivation and adherence to prehabilitation interventions. As a consequence, it was plausible that the effect of some outcomes such as functional capacity may be over estimated by reporting on motivated patients who are more likely to complete interventions.

1.7 Rationale for mechanistic trials in defining efficacy of prehabilitation

At the time of producing this thesis there were two large UK-based prehabilitation studies [54,55] currently recruiting patients (Westfit & Prepare ABC)[54,55]. Both studies aim to measure clinical outcomes such as length of hospital stay, functional capacity and post-operative complications. However, these studies have not been designed to investigate the underlying biological mechanisms that may be associated with any derived benefits. It is important

to investigate this as it may provide insights into whether certain molecular profiles confer a better or worse response to prehabilitation. This type of data would be useful when attempting to target interventions to patients most likely to benefit.

A mechanistic study would seek to investigate the physiological and biological changes associated with prehabilitation. A suitable study design would seek to clarify the complex cytokine-mediated signalling pathways that may be involved in improved fitness in these cancer cohorts. By correlating these observed biological differences with detailed body composition data, it may be possible to clarify the process by which prehabilitation can alter clinical outcomes.

1.7.1 The role of inflammation and cytokine signalling in tumourgenesis

Cytokines are a family of protein signalling molecules involved in various metabolic pathways and regulate both innate and adaptive immune responses[56]. In particular, the cytokines IL-6, IL-1β, and tumour necrosis factor (TNF) are known to have a central role in inflammation which appears to be a common feature among cancer patients[57]. It is suggested that IL-6 is released from different cell types in response to energetic stress (related to exercise) and inflammation. The mode (pulsed versus prolonged) of release of IL-6 has been shown to have different target organ effects (**figure 1-0**).

The role of inflammation in oncogenesis has been the subject of several mechanistic studies[58–60]. It is thought that while some inflammatory cytokines may promote tumour development and metastasis, others may have a protective effect[61]. In the case of colorectal cancer IL-6, IL-1 and TNF have been shown to promote tumour proliferation[62], while others such as IL10 and transforming growth factor-beta (TGFβ) have been shown to be protective[59]. In the case of TGFβ this protective function is thought to occur by inhibitory action on IL-6[59]. It is yet unknown as to whether prehabilitation has any immediate, medium or long- term effect on these inflammatory mediators. Some of the potential benefits would be clarification of the roles that cytokines may play in influencing clinical outcomes in prehabilitation.

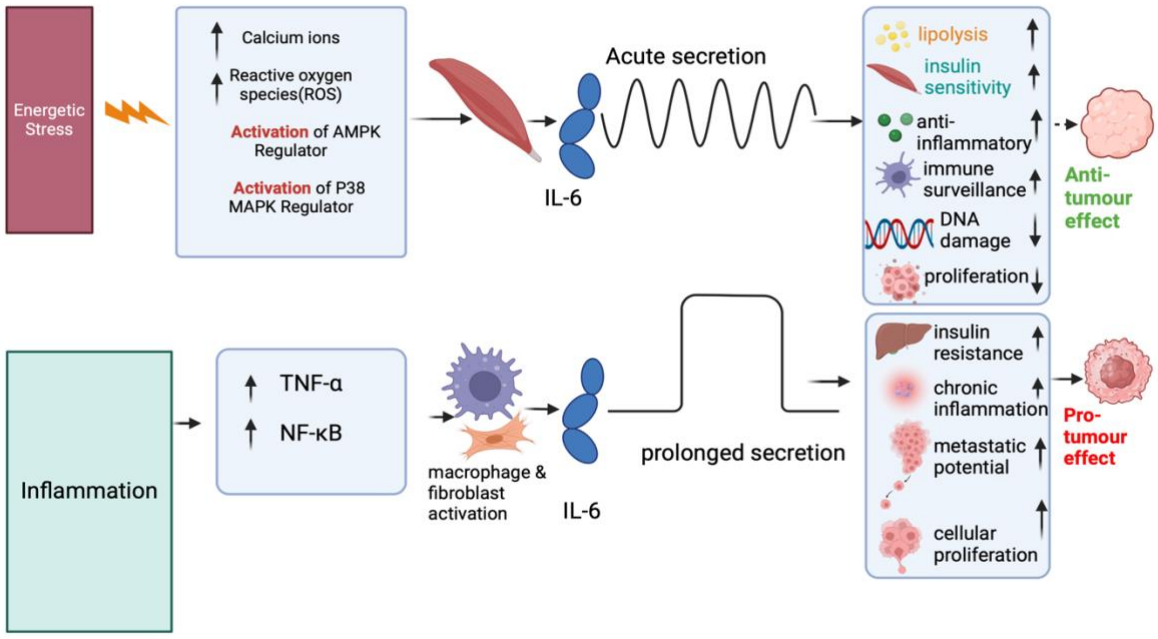


Figure 1-0 Biological response of IL-6 to exercise and inflammation. Energetic stress increases calcium ions and reactive oxygen species (ROS) and activates molecular pathways in exercising muscle; IL-6 is released acutely and induces an anti-tumour microenvironment. Inflammation is mediated by tumour necrosis factor (TNF) and activation of the Nuclear Factor κB regulatory pathway (NF-κB) ; there is prolonged IL-6 secretion which leads to chronic inflammation and a tumourgenic microenvironment.

1.7.2 The physiological adaptation to exercise

Previous work in colorectal cancer patients has shown that high intensity exercise does not appear to improve fitness[63,64] in some patient cohorts. It may be that this particular cohort of patients are not responsive to physical training. While the mechanism of this 'non-responder' effect is unclear, genetic and cancer related factors may play a role. It would therefore be worthwhile investigating whether there are inherent biological differences in these patient populations and other GI cancer patients in the way they might respond to prehabilitation interventions and in particular exercise training. This knowledge

may lead to the development of personalised medicine approaches based on a particular molecular fingerprint. In a time when NHS resources are stretched, if value may be gained from a targeted approach to prehabilitation interventions, it would be worth knowing how resources can be best targeted to achieve the desired results.

1.7.3 Prehabilitation and body composition

A novel component of this thesis is examining the effect of prehabilitation on body composition. Within the published literature, the effect of exercise on body composition has been well studied in the healthy sporting population, but not within the context of prehabilitation and cancer. Obesity as a risk factor for several cancers has been extensively studied, however, the molecular interplay that underpins poorer outcomes and the increased risk of recurrence is still poorly understood.

Epidemiological studies have consistently shown a positive correlation with increased body weight and colorectal cancer. It is thought that an aberrance in glucose homeostasis and associated insulin resistance may be the main common pathway in trying to understand what mechanisms lead to an increased risk of malignancy[65]. Studies also suggest that it is visceral rather than peripherally located subcutaneous fat that constitutes the main morphological feature associated with increased risk[66]. This may be because visceral fat is metabolically active and known to release adipokines that may play a role in the chemotactic spread of cancer cells[67].

Obese patients tend to be more sedentary. It therefore seems appropriate that a prehabilitation programme that focuses on improved carbohydrate metabolism and weight reduction may contribute to improved short and longer-term outcomes if new lifestyle changes can be sustained. Within this thesis the author will aim to assess whether changes in body composition brought about by prehabilitation has any influence on clinical outcomes.

Due to wide variations in the components and delivery of prehabilitation programmes, it was essential to determine where the gaps within the current

literature exist. This appraisal was achieved by conducting a synthesis of published data through a systematic review and meta-analysis of prehabilitation as an intervention in the patient group of interest.

1.8 The impact of prehabilitation on outcomes in hepatobiliary, colorectal and upper gastrointestinal surgery: A PRISMA-accordant meta-analysis

1.8.1 Abstract

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

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

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

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

test (P = 0.816) and no significant reduction in post-operative complications (P = 0.378) or mortality rates (P = 0.114).

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

1.8.2 Introduction

Recently, the focus around recovery following cancer surgery has shifted towards better preparation of patients for surgery[22,68]. While enhanced recovery after surgery is now standard post-operative care[11], several studies have suggested additional benefits from increasing the cardiorespiratory fitness of patients before surgery[7,69,70]. "Prehabilitation" has gained popularity as an umbrella term to describe physical exercise, nutritional, and psychosocial interventions to optimise physical and mental health prior to major surgery [71].

Recent systematic reviews have demonstrated that prehabilitation can reduce hospital length of stay in major non-cancer surgery (e.g. bariatric surgery) [72,73] but the benefit in hepatobiliary, colorectal, and upper gastrointestinal cancer is largely unknown. These cancer patients are a unique population characterised by different clinical outcomes, hospital length of stay, and surgical procedures. Indeed, these cancer patients may benefit significantly from nutrition and exercise programmes, as patients often present with weight loss (indicating malnourishment), and tend to be less physiologically fit than other cancer groups[74]. Collectively, this results in a hospital length of stay after oesophagectomy of 7-14 days[75], for example, whereas this is only 3.1 days after bariatric surgery [76]. Knowing whether prehabilitation reduces hospital length of stay or complication rates in cancer patients specifically is important because this can influence adjuvant therapy. Recent work has suggested that colorectal cancer patients are highly resistant to the benefits of exercise[77] and thus, examining the impact of exercise and nutrition on this population is valuable.

The two most frequently studied forms of prehabilitation are exercise and nutritional interventions. It has been shown that preoperative exercise increases fitness before operation and several studies have reported improvements in cardiopulmonary exercise test variables ($\dot{V}O_2$ max & anaerobic threshold) and functional capacity[3,24] after supervised and unsupervised pre-operative exercise programmes[78–80]. Several studies have reported that improved pre-operative fitness is associated with accelerated post-operative recovery following major abdominal surgery[20,81–84]. Benefits from prehabilitation include reduced hospital length of stay [12,85] and a reduced incidence of post-operative complications[19,48,86]. While no studies have reported exercise prehabilitation has a deleterious effect on post-operative outcomes, some studies have found no effect when prehabilitation is compared to standard care [3,19]. This may be a result of underpowered studies, "non-responder" effects to exercise [87], or that there is no clinically meaningful effect. Moreover, the response to prehabilitation is a complex phenomenon and whilst less fit patients are more likely to benefit most, prehabilitation does not guarantee good outcomes. Lastly, time to surgery is an independent factor that affects survival in cancer [88], and this is a major challenge to prehabilitation. Collectively, these data suggest exercise prehabilitation is capable of improving post-operative surgical outcomes, but the benefits to patients across studies and exercise-modalities remain to be determined.

Whilst there is evidence that poor nutritional status is an independent predictor of post-operative complications in colorectal cancer patients[33,89–91], there are few studies that have studied the possible benefits of nutritional prehabilitation for cancer surgery. It has been shown that under-nourished or 'at risk' patients are likely to have more post-operative complications [92], although the benefits are not always clear. Studies providing carbohydrate and protein supplementation in eucaloric populations pre-surgery have shown little benefit [93,94]. However, studies concerning protein provision have shown promising results including reduced hospital length of stay, lower rates of post-operative complications, and reduced readmission rates, regardless of baseline

nutritional status [95]. The net benefit of nutritional interventions before major cancer surgery remains to be determined.

Psychosocial interventions are often implemented as part of wider multimodal prehabilitation and aim to reduce stress and anxiety through education and counselling [3,9,22,43]. Further, studies have shown psychosocial interventions can augment improvements following exercise [96] or nutritional [97] interventions. Studies examining psychosocial-prehabilitation have, however, either not reported psychology-specific outcomes [22] or showed no significant improvement in anxiety and depression scores[3,9].

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

1.8.3 Methods

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines [98]. JL and LH independently conducted the eligibility assessment in an unblinded and standardised manner. Where there was disagreement, CG served as the final adjudicator. Once each database search was completed and manuscripts were sourced, all studies were downloaded into a single reference list with duplicates removed. Eligibility was assessed based on the criteria below. For eight of these studies, authors were contacted for supplementary data.

1.8.3.1 Literature search and study selection

A systematic literature search was conducted in Medline, Embase, and Cochrane databases with no start date but it included papers published to

December 18th, 2019. The search was performed within all fields and terms used were “prehabilitation” AND “peri-operative care” OR “perioperative care” AND “major surgery” OR, “colorectal” OR “hepatobiliary” OR “oesophagogastric” AND “outcomes” AND “complications”.

Studies that met the following criteria were included in this meta-analysis: (1) published as a full-text manuscript; (2) not a review or protocol manuscript; (3) studies involving patients undergoing elective colorectal, hepatopancreatobiliary, oesophagogastric cancer surgery, and colorectal resections for benign disease. All included studies were required to employ an intervention design and include at least one aspect of prehabilitation. Specifically, this included (i) an exercise programme for at least one week to include; aerobic, resistance, and concurrent exercise at all exercise intensities. Inspiratory muscle training (IMT) studies were also included in this category, as evidence suggests they can increase functional capacity [99] or (ii) nutritional supplementation. Three studies included in the meta-analysis provided psychosocial support including information and/or counselling in addition to the exercise and/or nutrition intervention. Additionally, descriptive data (e.g. sample size, mean, and standard deviation) must have been reported. Where these were not reported, details were requested from authors. The aim was to investigate the impact of prehabilitation on hospital length of stay, functional capacity (measured by the six-minute walk test [6MWT]), post-operative complications, and mortality rates in hepatobiliary, colorectal, and upper gastrointestinal cancer. Where studies measured multiple outcomes, they were treated as separate data points. Due to the small number of studies, subgroup analysis was not possible for the three cancer types or different exercise modalities.

Full text articles and supplementary data were reviewed to assess methodological quality of each study, using the PEDro scale (**Table 1.1**), which quantifies the methodological quality[100]. Before analysis, studies were further categorised into the primary and secondary outcomes that were recorded. To assess publication bias, funnel plots for each outcome variable were computed and the Trim and Fill method applied[101].

1.8.3.2 Outcomes

From each eligible article, data were extracted for hospital length of stay, functional capacity, post-operative complications, and mortality rates by prehabilitation intervention type. Interventions were grouped into three types (i) Multimodal prehabilitation: exercise, which included both nutrition and psychosocial support, (ii) bimodal prehabilitation: exercise and nutrition or psychosocial support, and (iii) unimodal prehabilitation: exercise or nutrition alone. Exercise interventions included were; aerobic, resistance, and concurrent exercise (combined aerobic/resistance exercise) at all exercise intensities. Regimes involving supervision by a kinesiologist or physiotherapist, and unsupervised home-based exercise regimes were included. Exercise intervention duration ranged from 1 week to 4 weeks and all interventions were within the current NHS surgery targets for cancer surgery[15]. It was our intention to summarise participant characteristics to determine if baseline fitness, clinical status, or nutrition status influenced outcome variables. However, due to absence of details in participant descriptions within the original investigations, this was not possible.

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

1.8.3.3 Data quality assessment and statistical analysis

In this meta-analysis, the cumulative effect of bias can lead to overstating or understating treatment effects. The Physiotherapy Evidence Database (PEDro) scale was used to assess the risk of bias of included studies [102]. Supplemental **table 1.1** shows how PEDro scores were assigned based on itemised criteria.

Random-effects meta-analyses were conducted, and comparisons were made between standard care and prehabilitation. For length of stay and functional capacity, raw difference in means was calculated, and for post-operative complications and mortality rates, the risk difference. Functional capacity was determined using 6MWT, as previously validated in this population[103]. Distance completed in meters was reported in all studies, and therefore the raw mean difference between standard care and prehabilitation was reported. Whilst functional capacity comprises a range of functional activities, the six-minute walking distance has been studied and considered a valid and reliable measure[103].

Hospital length of stay was reported in days from the date of operation to the date of discharge. The outcome measure for surgical complications was the number of Clavien-Dindo (CD) ≥ III complications reported[104]. Grade I & II were classified as minor complications and III & IV as major complications. These outcomes were selected as clinically meaningful endpoints in the majority (all studies reported at least 1 out of these 3 outcomes; length of stay, functional capacity, and complications) of published prehabilitation studies relevant to this review. Heterogeneity was quantified with the I^2 statistic. An I^2 value of 25% was interpreted as low, 50% as moderate and 75% as high between-study heterogeneity. To determine if the length of prehabilitation was an important factor in determining patient outcomes, the author completed linear regression analysis between the length of prehabilitation and hospital length of stay, functional capacity, post-operative complications, and mortality rates. Significance was set at $P < 0.05$ and data were analysed using GraphPad Prism (GraphPad Prism 8.0, GraphPad Software, Inc.).

Table 1.1 Characteristics of included studies

Reference	Intervention	Study Design	Outcome	Total patient number (n)	PEDro
Ausania et al, (2019)[4]	**Exercise** (supervised high intensity training & unsupervised functional exercises at home for ≥ 1 wk). **Nutrition** (liquid oral supplements, vitamins and pancreatic enzyme replacement)	**RCT** (standard group versus prehabilitation group)	POC, LoS, RR	40 (pancreaticoduodenectomy)	6
Barberan-Garcia et al, (2017)[9]	**Exercise** (high intensity interval training with cycle ergometer), **Psychosocial** (encouragement and motivation)	**RCT** (standard versus prehabilitation group	POC, LoS	125 (colorectal cancer, liver metastases, oesophagogastric resections)	8
Bousquet-Dion et al, (2018)[3]	**Exercise** (home-based & supervised (30 mins of moderate intensity aerobic training 3-4 d/wk to achieve 60-70% max heart rate. Resistance training (2 sets of 8-12 repetitions with resistance band targeting core muscles 3-4 d/wk) **Nutrition** (whey protein; Immunocal supplementation at 1.2g/kg body weight taken within 30 mins of exercise **Psychosocial:** stress and anxiety reduction strategies	**RCT** (supervised prehabilitation versus unsupervised rehabilitation)	6MWT	63 (colorectal cancer resections)	7
Carli et al, (2010)[20]	**Exercise** (light: walking and breathing exercises & moderate intensity cycling: 20 min/d increasing to 30min/d. 50% max heart rate increasing by 10%/wk for 4 wk. Resistance exercise combined with stretching: 3d/wk involving push-ups, sit-ups and lunges of 10-15 min duration.	**RCT** (walking/breathing exercise: standard versus prehabilitation: moderate aerobic and strength training)	6MWT	112 (colorectal cancer resections)	6
Chen et al, (2016)[22]	**Exercise** (20 min aerobic & 20 mins resistance training 3d/wk) at 50% max heart rate **Nutrition** (Whey protein supplementation 1.2g/kg)	**UCT** (match time control versus prehabilitation)	FC (6MWT)	116 (colorectal cancer resections)	3

	Psychosocial anxiety reduction measures with a trained psychologist and subsequently given video to practice at home				
Chia et al, (2016)[43]	**Exercise** (non-specific; cardiovascular and resistance exercise and increase in mobilisation from baseline levels (functional walking capacity) **Nutrition** (non-specific; to maintain weight with adequate calorie intake. **Psychosocial** (education)	**UCT** (retrospective matched control group versus prehabilitation group)	LoS, FC	117 (colorectal cancer resections)	3
Dunne et al, (2016)[7]	**Exercise** (interval moderate/high intensity 30 min cycling 3d/wk for 4wk	**RCT (**standard care versus prehabilitation)	$\dot{V}O_2$ max at AT, QoL, LoS	38 (colorectal liver metastases resections)	7
Gillis et al, (2014)[27]	**Exercise** (50 mins combined aerobic and resistance training. Home-based ≥ 3d/wk. **Nutrition** (1.2 g/kg whey protein; Immunocal supplementation)	**RCT** (standard care versus prehabilitation	6MWT, LoS, POC	77 (colorectal cancer resections)	7
Gillis et al, (2016)[8]	**Nutrition** (whey protein; Immunocal 1.2.1.5 g/kg)	**RCT** (nutritional counselling with whey protein versus counselling with placebo)	6MWT	48 (colorectal cancer resections)	8
Janssen et al, (2019)[18]	**Exercise** (aerobic and resistance training- not specified) **Nutrition** (1.2 g/kg protein supplementation + 30% increase in baseline calorie intake)	**UCT** (retrospectively selected control vs prehabilitation group	Delirium, LoS, MO, POC	627 (colorectal cancer resection and abdominal aortic aneurysm repair)	3
Kim et al, (2009)[78]	**Exercise** (structured aerobic training to 40-60% max heart rate, 3-4 wk for a total of nine sessions)	**RCT** (standard care versus prehabilitation)	6MWT	21 (colorectal cancer and inflammatory bowel disease resections)	5
Kitahata et al, (2018)[105]	**Exercise** (aerobic exercise at 65 % V̇O2 max combined with resistance exercise: 2 sets of squats 300 reps) varied based on participants fitness. All performed twice daily, 1 wk before surgery	**UCT** (consecutive patients assigned to standard vs prehabilitation)	LoS, POC, MO	576 (pancreatic cancer resections)	4

Mazzola et al, (2017)[19]	**Exercise** (incentive spirometry 3 sessions/d and 30 mins moderate intensity walking 3d/wk) **Nutrition** (oral immuno- nutritional supplementation 5-7 d preoperatively +/-naso-jejunal feeding +/- total parenteral nutrition)	**UCT** (retrospectively selected match group versus prospectively assigned prehabilitation group)	LoS, MO, POC, RR	76 (pancreatic, gastric and oesophageal resections)	4
Minnella et al, (2018) [17]	**Exercise** (Aerobic: 30 mins moderate- Borg 12-13, continuous training 3d/wk. Resistance exercise: moderate intensity; 3 sets of 8-12 repetitions with resistance band 1d/wk). **Nutrition** (dietary advice & Whey protein supplementation, Immunocal 1.2-1.5g/kg ideal body weight) to provide ~20% of total energy requirements. Given to all in intervention group regardless of nutritional status	**RCT** (standard care as per enhanced recovery after surgery protocol versus prehabilitation)	6MWT, LoS, POC, RR, FC	49 (oesophagogastric resections)	8
Nakajima et al, (2019)[12]	**Exercise** (60 mins/d, 3d/wk moderate intensity aerobic training; modified Borg scale score 3-4. Resistance exercise (two sets of 10 reps of squats, calf raises, bridge-ups, arm movements) **Nutrition (**leucine-rich amino acid L40) 30 mins after start and end of exercise.	**UCT** (propensity-matched historical control versus prehabilitation group)	LoS, POC	152 (Liver resection ≥ 3 Couinaud segments & pancreaticoduodenectomy)	4

*RCT = randomised controlled trial; UCT = uncontrolled trial; LoS = Length of Stay; FC= Functional Capacity; QoL = Quality of Life; POC = Post-operative complications (Clavien-Dindo ≥III); MO = 30-day mortality; RR = Re-admission rates; 6MWT = 6-minute walking test; $\dot{V}O_2$ max at AT = maximal oxygen uptake at anaerobic threshold.

1.8.3.4 PRISMA

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) provides a framework for minimum reporting standards for systematic reviews and meta-analyses[106]. Figure 1-1 . below provides a PRISMA-accordant schematic on how studies were selected.

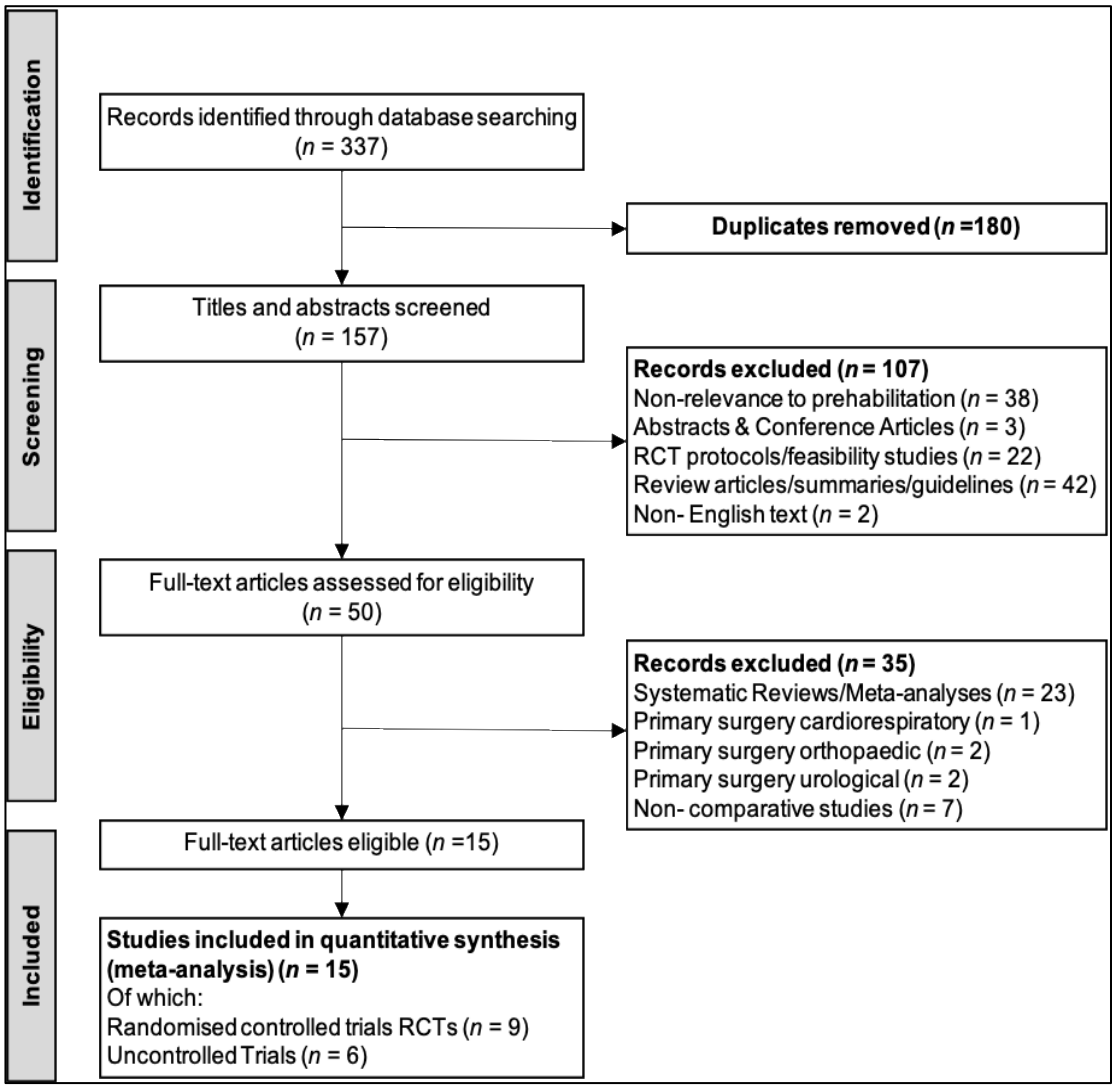


Figure 1-1 . PRISMA flowchart of studies selected for the Systematic Review and meta-analysis.

1.9 Results

1.9.1 Study selection

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

1.9.2 Study characteristics

Of the 15 studies included, nine were randomised controlled trials and six were uncontrolled trials. Three studies examined the effect of multimodal prehabilitation, seven studies examined bimodal prehabilitation, and five studies examined unimodal prehabilitation. For grouping studies together, it was important to assess the type, duration and intensity of exercise across studies using exercise as prehabilitation. Although type, intensity and frequency of exercise varied between studies, most reported achieving $\geq$ 50% maximum heart rate. In one study where two exercise interventions (low intensity vs moderate intensity/strength training)[107] were compared, the low intensity unsupervised exercise intervention was treated as the 'standard'. The meta-analysis was run with and without this study and no difference in overall outcome was observed. In studies where nutrition was utilised, nutritional optimisation was homogenous and standardised amongst studies at 1.2-1.5 g protein/kg body mass.

1.9.3 The effect of prehabilitation on hospital length of stay

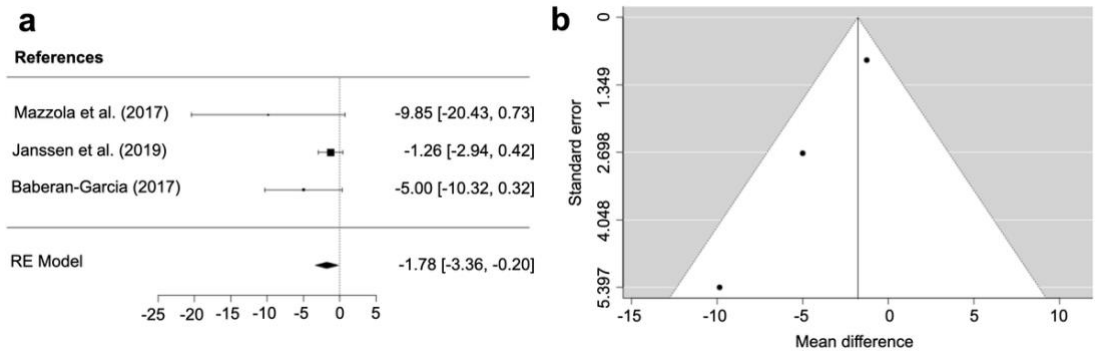


Figure 1-2 (a) Forest plot showing the effects of prehabilitation on length of stay. A negative value represents a shorter length of hospital stay in prehabilitation groups compared to standard care (b) Funnel plot of studies evaluating the effect of prehabilitation on hospital length of stay.

Three studies investigated hospital length of stay and observed a significant reduction of 1.78 days (95 % CI:0.2, 3.36, P <0.05), **figure 1-2**. There was low heterogeneity (I^2 <0.001%) amongst studies reporting this outcome. The small number of studies limits assessment of plot symmetry and bias. Linear regression analysis showed there was no significant relationship between length of prehabilitation and hospital length of stay (R^2 = 0.99, P >0.05).

1.9.4 The effect of prehabilitation on functional capacity

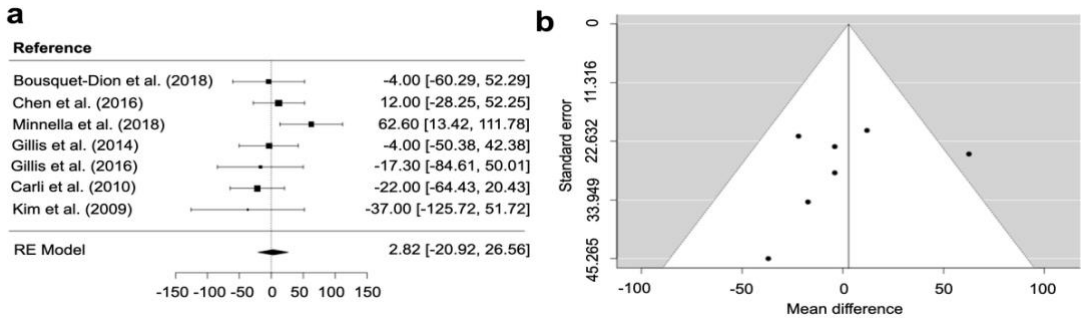


Figure 1-3 (a) Forest plot showing the effect of prehabilitation on functional capacity (6MWT). A positive value denotes a greater distance covered in

prehabilitation groups compared to standard care (b) Funnel plot of studies evaluating the effect of prehabilitation on functional capacity.

Seven studies examined the impact of prehabilitation on functional capacity, measured by the 6MWT. There was no significant difference in functional capacity with prehabilitation (+2.82 m, 95 % CI: -20.92, 26.56, P = 0.816) **figure 1-3**. There was a moderate level of heterogeneity (I^2 = 31.19%). The small number of studies limits an assessment of symmetry and bias. Linear regression analysis showed there was no significant relationship between length of prehabilitation and change in functional capacity (R^2 = 0.24, P >0.05).

1.9.5 The effect of prehabilitation on post-operative complications

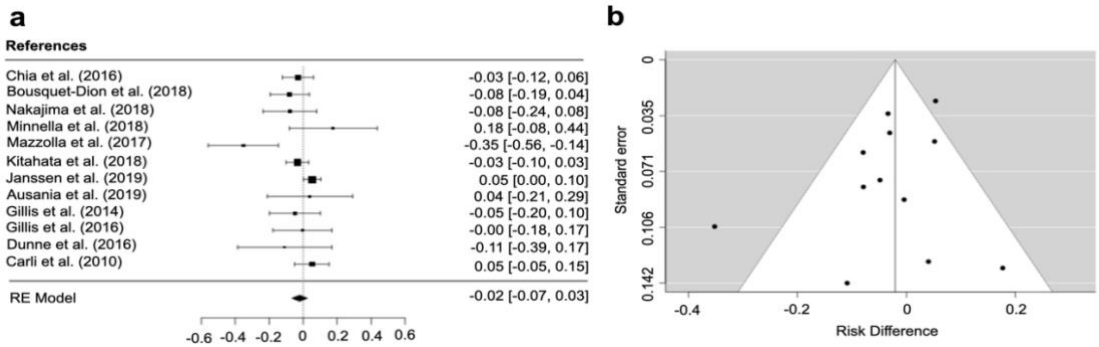


Figure 1-4 (a) Forest plot showing the impact of prehabilitation on Clavien-Dindo ≥ III complications. A negative value denotes a lower risk in prehabilitation groups compared to standard care groups (b) Funnel plot of studies showing the effect of prehabilitation on post-operative complications.

The author examined the effect of prehabilitation on grade III & IV Clavien-Dindo post-operative complications as a lower rate of surgical complications might explain reduced hospital length of stay. The overall risk difference in post-operative complications was -0.02 (95 % CI = -0.07, 0.03; P = 0.378;) **figure 1-4** indicating that there was no significant reduction in the risk of clinically important post-operative complications following prehabilitation. There was a

moderate level of heterogeneity (I^2 = 39.73%). The funnel plot demonstrates some symmetry which suggests low level of publication bias. Linear regression analysis showed there was no significant relationship between length of prehabilitation and post-operative complication rates (R^2 = 0.05, P >0.05).

1.9.6 The effect of prehabilitation on mortality rate

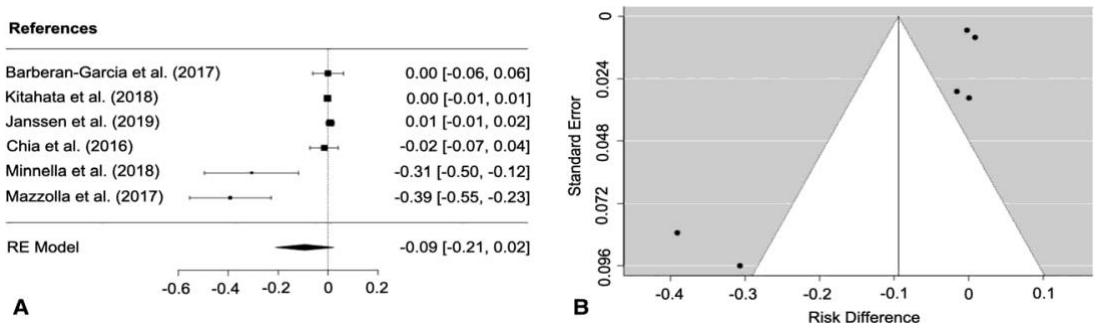


Figure 1-5 (A) Forest plot showing the impact of prehabilitation on mortality . (B) Funnel plot of studies showing the effect of prehabilitation on mortality.

Mortality was reported in eight of fifteen studies, although two studies reported no deaths in the monitoring period and thus were excluded from the meta-analysis. The remaining six studies all recorded 30-day mortality, while one study additionally reported 90-day mortality. The overall risk difference in mortality rates was -0.09 (95% CI = -0.21, 0.02, P = 0.114) **figure1-5** indicating there was no significant effect of prehabilitation on mortality rates. There was a high level of heterogeneity (I^2 = 98.95%). Linear regression analysis showed there was no significant relationship between length of prehabilitation and mortality rates (R^2 = 0.007, P >0.05).

1.9.7 Summary of the effect of prehabilitation on outcomes

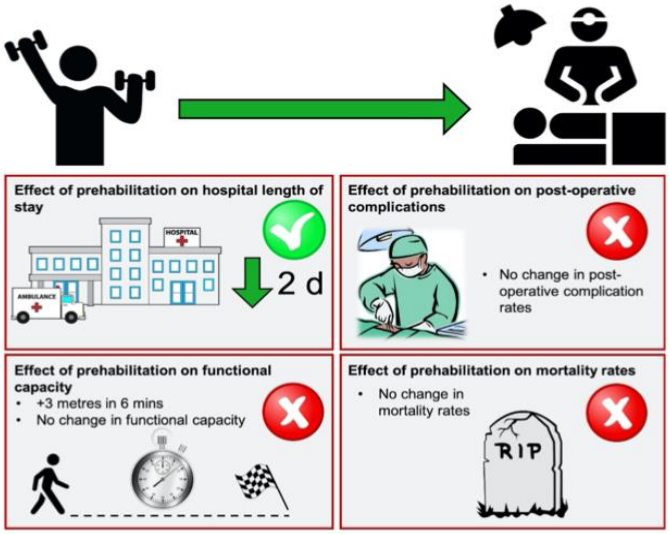


Figure 1-6 Prehabilitation reduced length of hospital stay by 2 days but had no effect on post-operative complications, functional capacity or mortality.

1.10 Discussion

1.10.1 Overall effect of all prehabilitation modalities

The main finding from this meta-analysis was a statistically significant reduction in hospital length of stay with a mean reduction of 1.8 days with prehabilitation. The randomised controlled trial by Barberan-Garcia et al. employed a combination of high intensity training and psychosocial motivational coaching in a population undergoing curative colorectal, liver resections, and oesophagogastric resections[108]. This study was deemed high quality and registered eight on the PEDro scale. The largest uncontrolled trial of 627 patients (77% of which were colorectal resections) used a combination of aerobic/resistance training and protein supplementation[18]. The smallest uncontrolled trial comprising pancreatic and oesophagogastric resections employed a combination of incentive spirometry, moderate intensity exercise and protein supplementation[19]. These two studies achieved lower PEDro scores of three and four, respectively. From the data it was not possible to

ascertain which aspect of prehabilitation had the largest influence on the reduced hospital length of stay. In most clinical settings this phenomenon is often multifactorial, however, the data from individual studies[9,105] suggests reduced complication rates may explain the reduced hospital length of stay, although this was not confirmed in this meta-analysis. In their study of pancreaticoduodenectomies Kitahata et al. showed no difference in operation-specific complications such as delayed gastric emptying or leak rates between prehabilitation and standard care. However, the prehabilitation group had a significantly reduced median hospital length of stay (16 vs. 24 days) due to lower pulmonary complications[105].

Of the fifteen studies, eight assessed functional capacity as measured by the 6MWT. There were four[8,17,27,109] moderate to high quality studies (PEDro ≥ 7). There was some variation between the studies with respect to the distance at which the 6MWT was deemed clinically meaningful. For example, one study set a threshold distance of 20 metre walking distance improvement from baseline as clinically significant[110], which was based on a prior study by Antonescu et al.[111] estimating minimally clinically important differences in patients undergoing abdominal surgery. This was not specific to cancer surgery. Another study suggested that a distance improvement of at least 19 metres had to be reached[5]. This distance was thought to be clinically meaningful as it represented the measurement error in this patient cohort[112]. All four studies reported an improvement in walking distance in the prehabilitation group compared to standard care. However, this effect was sustained at 4 and 8 weeks post-operatively in only two[17,27] out of the four studies. This suggests that sustained improvements in functional capacity may relate to the type of surgery and the timing of measurements after prehabilitation (before/after surgery). Additionally, benchmarks for clinically relevant improvements may be different for different studies involving the same type of surgery. This presents a challenge in pooling functional capacity data.

While some individual studies examined reported a statistically significant improvement in functional capacity, this was not replicated in our pooled analysis. The optimum type, duration, frequency, and intensity of exercise

required to observe improvements in functional capacity within this patient cohort remains elusive.

It is also unclear what the contribution of nutrition would be to the observed overall effects. A single study by Gillis et al. used unimodal prehabilitation with nutrition counselling and whey protein supplementation[110]. In this study, although an improvement in the 6MWT was observed, it was not statistically significant. The variability in response of functional capacity probably supports a tailored prehabilitation approach[113] for different types of cancer surgery. Due to the variability in exercise types, frequency, and duration it was not possible to group cancer types together to arrive at a combined effect for functional capacity. This is pertinent in cases where physiological/biological differences may affect the response to prehabilitation strategies[114,115] as well as the effect of neoadjuvant chemotherapy [116], long/short course chemoradiation [117], and pre-operative jaundice [118].

The duration of prehabilitation interventions ranged from one week [105] to six weeks[12]. In this meta-analysis, there was no statistically significant relationships between the duration of prehabilitation and the improvement in patient outcomes. However, when examining hospital length of stay, there was a strong (although non-significant) correlation (R^2 = 0.99) where shorter periods of prehabilitation promoted greater reductions in hospital length of stay [18]. More studies using different lengths of prehabilitation are required to determine if this relationship is significant. Prehabilitation interventions are constrained by National Health Service cancer waiting targets (or equivalent) but encouragingly, the results from this study suggest as little as one week can benefit patient outcomes.

1.10.2 Effect of prehabilitation in hepato-pancreato-biliary (HPB) cancer surgery

There was a total of 842 patients from six studies[12,19,80,105,108,119] that used different combinations of multimodal, bimodal, and unimodal prehabilitation. The published data suggests that prehabilitation in HPB cancer surgery results

in reduced hospital length of stay, fewer post-operative complications and preservation of gastric function, although these results have not been consistent between studies. Nakajima et al. compared a prehabilitation group (exercise and nutrition) with a matched historical cohort and showed significant reductions in hospital length of stay in the prehabilitation group[12]. In a similar study design involving the analysis of a retrospective control group compared to an exercise and nutrition prehabilitation group, a reduced hospital length of stay was not observed but there was a significant reduction in Clavien Dindo ≥ III post-operative complications[19]. This finding was replicated in another study which randomised patients to standard care or high intensity exercise and motivational interviews as the prehabilitation intervention[108]. The authors reported a significant reduction in post-operative complications, possibly explained by an increase in aerobic capacity.

In contrast Ausania et al. employed nutrition (liquid protein/carbohydrate and enzyme replacement) and exercise prehabilitation in a total cohort of 40 patients undergoing pancreaticoduodenectomy. There was no difference in post-operative complications (pancreatic leak) and hospital length of stay. However, a significant reduction in delayed gastric emptying was found in the prehabilitation group[120]. This finding may suggest that prehabilitation might improve underlying physiology[121], however, it does not translate to reduced complication rates and length of stay with the number of patients studied. If prehabilitation does improve underlying physiology, the specifics and mechanisms remain to be determined. In a large retrospective series of 576 pancreaticoduodenectomies, Kitahata et al. reported a significant reduction in pulmonary complication rates and length of stay within a supervised exercise prehabilitation programme compared to standard care historical cohort[105]. However, there was no difference in the incidence of operation specific complications such as pancreatic/biliary leak rates and specifically delayed gastric emptying as observed by Ausania et al [4].

Dunne at al.[7] examined aerobic capacity using cardiopulmonary exercise testing data in patients undergoing colorectal liver metastases resections. A four-week exercise prehabilitation programme significantly improved maximal

oxygen uptake and anaerobic threshold, and quality of life, compared to a control group[80]. Collectively, these data suggest that as little as four weeks of exercise prehabilitation can exert clinically significant benefits for patients.

1.10.3 Effect of prehabilitation in colorectal cancer surgery

Prehabilitation studies concerning colorectal cancer have had mixed results, whereby some studies reported reduced hospital length of stay or improvements in functional capacity, but others have not. In the body of literature reviewed, there appears to be no evidence for improvement in post-operative complications in colorectal cancer with prehabilitation. There was no difference in operation-specific colorectal complications such as anastomotic leak, ileus, or wound infection[122].

A total of 1113 patients from nine studies[18,70,107–110,123–125] employed prehabilitation modalities. Chia et al. focused on a group of frail patients undergoing colorectal resections and employed a multimodal prehabilitation programme. Authors reported a reduced length of stay, although there were no differences in complication rates and 30-day mortality[123]. Bousquet-Dion et al. assessed functional capacity and found that prehabilitation made no difference to this measure. However, patients deemed most likely to show improvements were the sedentary cohorts as defined by the Community Healthy Activity Model Programme for Seniors questionnaire[109,126]. In a larger study involving 484 colorectal resections, Janssen et al. showed significant reductions in peri-operative delirium but there was no difference in length of stay, complications and 30-day mortality[18]. In two separate studies[110,124] involving unimodal and multimodal prehabilitation respectively, a significant improvement in functional capacity was reported with moderate and high intensity exercise, although these have also been observed in low intensity exercise[107]. These data suggest that there may be metabolic and physiological differences between patients that influence responses to prehabilitation interventions[115,127]. This raises a further question of how to select patients that might benefit the most from prehabilitation.

1.10.4 Effect of prehabilitation in upper gastrointestinal cancer surgery

Prehabilitation for upper gastrointestinal cancer surgery has led to improvements in functional capacity and reductions in post-operative complications. Our analysis is based on a group of 120 patients from three studies[19,108,128]. Minnella et al. studied 49 oesophagogastric resections and reported a significant improvement in functional capacity[128]. Mazzola et al. found a reduction in post-operative complications (Clavien-Dindo $\geq$ III) in patients enrolled on a prehabilitation programme[19]. Although Barberan et al. [108] also reported similar significant reductions in serious post-operative complications, it was not possible to isolate outcomes for upper gastrointestinal surgery patients as the group was combined with both colorectal and HPB surgery in the study. Overall, there was no difference in hospital length of stay between the standard and prehabilitation groups.

1.10.5 Strengths & Limitations

In this study, the author has been able to perform a comprehensive review of the impact of prehabilitation in HPB, colorectal, and upper-gastrointestinal surgery. Using PEDro scoring, the author has managed to assess quality of included studies. However, this study is not without limitations. The most pertinent limitation of this meta-analysis was the paucity of randomised controlled trials[129]. There were nine randomised controlled trials with a PEDro score ranging 5-8, which made evaluating the efficacy of prehabilitation challenging[130]. For the exercise interventions, there were not enough studies to allow pooling of low, moderate, and high intensity exercise subgroups. These details would allow the determination of the minimum amount, type, intensity, and frequency of aerobic/strength training to improve functional capacity or clinical outcomes. Likewise, although most nutrition interventions involved protein or carbohydrate supplementation, the variability in compliance likely rendered any additive or individual effect of nutrition inconclusive[131].

Another limitation of the literature in this field is the lack of detail in reporting. Few studies reported objective measures of exercise intensity and volume.

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

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

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

1.11 Conclusion

Prehabilitation can effectively reduce hospital length of stay in hepatobiliary, colorectal, and upper gastrointestinal cancer surgery (**figure 1-6**). There is a lack of randomised controlled trials in this population (n = 9), of which only three scored 8 or greater on the PEDro scale and two of the studies contained only

48 and 49 patients, respectively. Thus, there is a need for larger, high quality randomised controlled trials to expand the evidence base for adoption and implementation of prehabilitation programmes and provide statistical sensitivity for low incidence measures such as mortality. In particular, the type, duration, frequency, and intensity of exercise intervention needs to be standardised. Secondly, training variables appropriate for each cancer type require further examination. To improve quality and rigour of future investigations, measurement of discrete variables such as cardiopulmonary exercise test parameters[132] pre- and post-prehabilitation may provide a standardised basis for analysing improvements in cardiorespiratory fitness, which would avoid the apparent variability in selection of a clinically meaningful benchmark for improvement in functional capacity. This will be addressed in detail in the SPECS Trial chapter. Future studies should focus on identifying patients who would benefit most from prehabilitation and the mechanistic underpinning of any improvement in clinical outcomes. Studies should closely monitor nutrition intake to determine if the response to exercise prehabilitation is dependent upon nutritional status. Lastly, mortality should be monitored for 12 months post-surgery to determine if prehabilitation has any affect beyond 90 days.

1.12 Scientific basis and aim of this thesis.

1.12.1 Aims

This thesis will examine the efficacy of prehabilitation in the context of elective cancer surgery for colorectal and colorectal liver metastases. Efficacy will be determined by analysing patients' physiological and biological responses to an exercise-based prehabilitation programme.

1.12.2 Hypothesis

The author hypothesises that prehabilitation may improve clinical outcomes by altering patients' physiological fitness through a mechanism involving changes in the inflammatory cytokine profile, augmented cardiovascular resilience, weight reduction and lean muscle mass building. Additionally, prehabilitation

may improve psychological conditioning and physical well-being in patients undergoing elective major cancer surgery.

1.12.3 Hypothesis Testing

Alterations in cardiorespiratory physiology will be determined by measuring changes in CPET parameters before and after prehabilitation. Biological adaptation to prehabilitation will be determined by measuring biochemical markers and variations in anti/pro inflammatory circulatory cytokines before and after prehabilitation. The effect of prehabilitation on handgrip strength and body composition will be assessed by DXA scanning to investigate any correlation between muscle/fat ratios and clinical outcomes. Validated questionnaires will be used to gain an understanding of the psychological adaptation of patients to prehabilitation.

Chapter 2: CPET Data Analysis

A comparative analysis of cardiopulmonary exercise testing variables and oncological factors predictive of survival in major colorectal & hepatopancreatobiliary cancer surgery

2.1 Introduction

Cardiopulmonary Exercise Testing (CPET) can be used to objectively quantify the risk of peri-operative complications after major surgery[25]. Within the context of perioperative risk and surgical planning, some of the derived variables such as peak oxygen consumption ($\dot{V}O_2$ peak/max)[133], anaerobic threshold (AT)[134,135], and ventilatory equivalent for carbon dioxide (VE/VCO_2)[136] have been most frequently studied and are thought to predict peri-operative outcomes most accurately. The interpretation of these values have been used to guide peri-operative patient discussions. When used in conjunction with other risk predicting tools such as the Carlisle calculator[137], these measures may form the basis for consent and more meaningful discussion of risk with patients. Additional information may be gained to initiate operative optimisation, high dependency and critical care resource allocation and overall risk stratification[138].

Different cancers may pose different physiological demands on the body and may affect performance at CPET. The effect of anaemia and biliary obstruction which are common biochemical aberrations in colorectal (CR) and hepatopancreatobiliary (HPB) cancers, respectively, are known to impact CPET variables[141,142]. Additionally, patients with gastrointestinal (GI) cancers are often challenged with undernourishment as a direct obstructive consequence of a growing tumour with associated 'cancer wasting' effects[143,144]. The overall prevalence of sarcopenia in this patient population was reported as high as 43% in a recent systematic review[145]. The above factors individually and collectively may affect CPET performance. Given that these biochemical factors are unique to certain types of cancer, it is unclear whether certain CPET variables are

better predictors of outcomes or are more prognostically sensitive for certain cancers. Chmelo et al, have recently shown a high VE/VCO_2 being predictive of poorer survival in oesophagogastric cancer[136]. To date, there has not been a comparison of $\dot{V}O_2$ peak/max, AT and VE/VCO_2, and their sensitivities in predicting survival in CR and HPB cancer surgery. Due to general physiological deconditioning, cancer patients are unlikely to see a plateau in their oxygen uptake and as such VO_2 peak rather than VO_2 max will be used throughout this thesis. The aim of this analysis was to screen a CPET database from a major tertiary care centre to determine which of these three variables was most accurate in predicting survival after major CR and HPB cancer surgery. The overall objective of performing this analysis was to assess a similar retrospective cohort to the SPECS trial, to determine whether there are any cancer-related demographics that influence CPET performance.

2.2 Colorectal Cancer

The term ‘colorectal’ denotes any primary cancer arising from the anatomical regions of the rectum and colon (**figure 2-0 A**). It is believed that the pathogenesis process begins with a polypoid growth that progresses to dysplastic adenomas, then to invasive adenocarcinoma[146] (**figure 2-0 B**). If left untreated, invasive adenocarcinomas may spread to regional nodes and to other organs such as the liver and lungs.

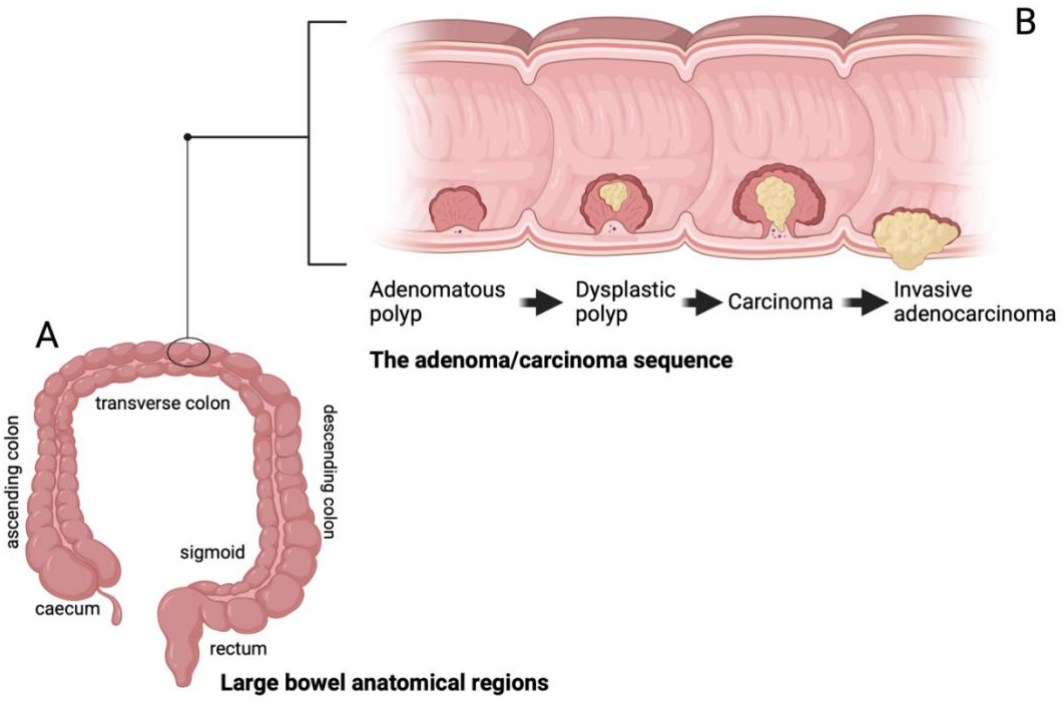


Figure 2-0 (A) Anatomical large bowel regions & (B) adenoma/carcinoma sequence

For patients included in this analysis, colorectal cancers were diagnosed by a combination of computed tomography (CT) imaging and histology confirmed pre-operatively via endoscopic evaluation. For locally advanced and T4 stage colonic lesions, a decision on neoadjuvant therapy (NAT) was determined taking patient wishes, oncological considerations, and overall fitness into consideration as determined by the colorectal multidisciplinary team (MDT). Rectal cancers were further staged with magnetic resonance imaging (MRI). Locally advanced rectal cancers and those with threatened circumferential resection margins (CRM) underwent long or short course chemoradiotherapy and were restaged prior to operative management. All patients were discussed at a weekly MDT meeting where management plans were documented as standard. Operative details were standardised and performed by a team of eight colorectal surgeons. The operative modality (minimally invasive or open approach) was left to the discretion of the operating surgeon and individual skillset. All patients were enrolled on an enhanced recovery as standard[147].

2.2.1 Colorectal Liver Metastases

The liver is the most common site for metastases from the colorectal cancers and occurs in 80% of patients[148]. The spread of colorectal cancers occurs via the bloodstream and lymphatic system (**figure 2-1**). This spread to the liver may be synchronous (occurring within 6 months of the primary colorectal cancer) or metachronous (occurring after 6 months)[149]. In 40% of patients the liver is the sole metastatic site thereby presenting the opportunity for curative surgical intervention.

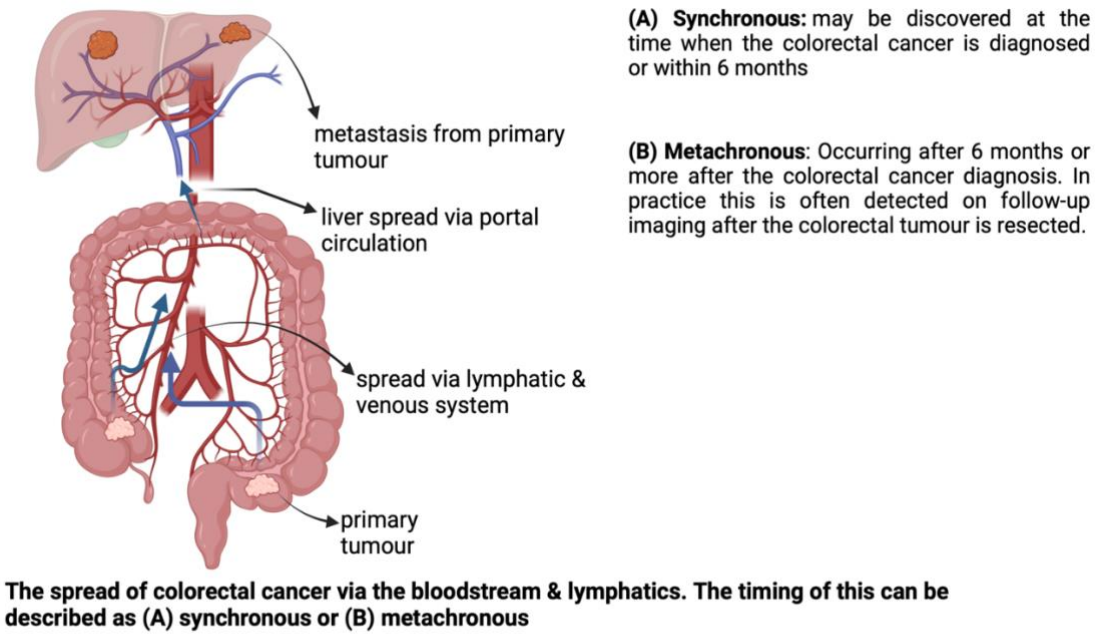


Figure 2-1. Colorectal liver metastases: Colorectal cancers may spread via the blood stream or lymphatics to distant sites such as the liver.

2.2.2 Defining Resectability

Prior to the advent of modern management modalities for CRLM, heavy disease burden in terms of size and number of lesions or disease close to the liver inflow

and outflow vessels often rendered the disease unsuitable for curative resection. Our current understanding of resectability is determined by whether sufficient future liver remnant (FLR) with adequate inflow , outflow and biliary drainage is achievable. Future liver remnant can be defined as the remaining functioning liver after major hepatectomy. As a general rule, 30% of FLR is required for normal livers. This value increases to 35% and 40% for post-chemotherapy and cirrhotic livers respectively.

2.2.3 Modern management techniques

Over the last decade, there has been a paradigm shift away from major anatomical segmental resection in favour of parenchymal preservation[150]. This thinking is rooted in the knowledge that up to 50% of CRLM recur within2 years of the index operation and repeat resections are often required if deemed resectable. A number of parenchymal-reserving techniques are currently employed. Non-anatomical resections and metastasectomies achieve parenchymal sparing by preserving major inflow and outflow pedicles while aiming for at least a 1mm margin of clearance from the lesion. This may also be achieved through radiological interventions such as radiofrequency or microwave ablation and in some specialised centres stereotactic ablative body radiotherapy (SABR).

Other surgical based techniques include two-stage hepatectomies, often for bilobar disease. The first stage involves metastasectomies in the left lobe combined with right portal vein ligation, with the aim of achieving hypertrophy of the ipsilateral lobe prior to removal of the contralateral lobe at the second stage. Within the first stage, studies have demonstrated that radiological portal vein (PVE) +/- hepatic vein embolisation (HVE) may achieve a greater degree of hypertrophy than surgical ligation[151]. These techniques aim to increase the FLR to facilitate safe resection to reduce the risk of post-hepatectomy liver failure. For the purposes of this analysis liver surgery included only CRLM resections and not primary liver tumours. Major and minor resections were defined by the International Study Group for Liver Surgery (ISGLS) criteria. CRLM were diagnosed using dual imaging modalities of CT and MRI. Operative

management followed an identical practice as for colorectal resections. The enhanced recovery programme for liver surgery began in 2016, as a result the majority of patients (37) 67% in this series did not participate in this service.

2.3 Pancreatic Cancers

Pancreatic cancer presents a significant challenge to healthcare professionals as mortality rates have narrowly improved over the last 50 years[152]. It is thought that the pathogenesis involves the activation of oncogenes and de-activation of tumour suppressor genes, combined with aberration from various signalling pathways to cause malignant transformation of pancreatic ductal epithelium[153]. There are two main types of pancreatic tumours; those arising from the exocrine cells (85%) and neuroendocrine tumours arising from the endocrine cells (<5%)[154]. Patients often present at an advanced stage in the disease course and consequentially only 15-20% of patients presenting with pancreatic cancer are deemed potentially curable through surgery[155]. Of patients undergoing potentially curative management 5-year survival rates are <10%[156]. One of the main reasons for the lethality of this cancer may be the fact that it is often diagnosed late. Currently no reliable screening programmes exist and even where curative resection is achieved, recurrence in most patient occurs within two years[157]. This observation underlines both low rates of early diagnosis and aggressive tumour biology that is incompletely understood in terms of the factors that promote spread and influence local recurrence. Within our analysis, pancreatic cancers were excluded due to the relatively high proportion of patients who either declined surgery, had a poor CPET result or were found to have metastases at operation.

2.3.1 The role of pre-operative biliary drainage

Malignant hyperbilirubinaemia is associated with physiological aberrations that may lead to poorer CPET performance and subsequently increased morbidity and mortality in patients undergoing HPB cancer resections. In current clinical practice the decision on drainage often rests on factors such as presence of other comorbidities such as renal failure, concurrent biliary tract infection, timing

of surgery and whether NAT is being considered. Several observational studies have analysed and compared patient cohorts that have undergone pre-operative drainage with matched cohorts that have undergone resection without drainage. The data concerning this is conflicting with some reports suggesting no difference[158], others demonstrating improved outcomes with drainage[159], while a Cochrane Review has shown worse outcomes mainly because of complications such as bleeding and infection[160].

2.4 The utility of CPET in GI Cancers

With colorectal cancer being the third most common cancer and increasingly more patients being eligible for liver resection from colorectal metastases, GI cancer represent a large proportion of the NHS operative workload. With the advances in chemotherapy, radiotherapy, minimally invasive operative platforms, prehabilitation and peri-operative care the selection criteria for major cancer resection has been expanding. More physiologically challenged patients are increasingly being considered for moderate to high risk resectional procedures. As the use of CPET within this patient cohort increases, so too will be the need to better understand how the test can be best utilised in bespoke patient populations.

CPET use in perioperative risk stratification has increased over the last decade[161]. Several studies involving colorectal[162] and hepatobiliary[163,164] patient cohorts have reported an association between suboptimal CPET values and increased risk of morbidity and mortality. CPET involves the objective measurement of patients' functional capacity by combining data from a 12- lead electrocardiogram, heart rate, pulse oximetry, metabolic gaseous exchange analysis, and non-invasive blood pressure measurements. These values are computed together to give graphical analyses of exercise capacity and several variables are both directly measured and indirectly derived. These are typically displayed as the Wasserman nine panel plot (ref). The purpose of the test is to replicate the physiological stress induced by surgery to predict peri-operative outcomes.

National Institute of Clinical Excellence (NICE) recommends CPET as an adjunct to other clinical assessment tools in patients over sixty undergoing major surgery[165]. However, there has been considerable debate over quality and validity of the published evidence for the use of CPET as a standalone predictive tool[165]. One of the central arguments advanced was that different variables may be more relevant for different types of major surgery. For example, lung function and aerobic capacity are more relevant measures for a patient undergoing lung surgery, whereas the anaerobic threshold is perhaps a more appropriate measure of fitness for someone undergoing a pancreaticoduodenectomy. Even when factoring in this important consideration, the administration and interpretation of the test may lead to variability in determining test outcomes in patients with similar levels of fitness thereby mis-categorisation of risk profiles. Additionally, several studies have highlighted the impact of confounders in patients' performance. Particularly for GI surgery, some of these include the effect of anaemia, body mass index and jaundice[165]. This observation may mean that this sort of physiological deconditioning may be transient and relevant at the time of testing but not necessarily predictive of mortality or longer-term outcomes.

2.4.1 Cancer-related factors affecting CPET performance

Patients with GI cancers frequently present with symptoms such as abdominal pain, change in bowel habit, rectal bleeding, anaemia, jaundice, and weight loss[166]. The physiological changes brought on by signs such a reduction in lean body mass, anaemia and jaundice may have a profound impact on CPET variables, often towards poorer performance. Malnutrition as a consequence of reduced oral intake and sarcopenia mediated through inflammatory signalling pathways, may lead to reduced exertional and respiratory effort with the consequence of an inability to complete the test or early exhaustion. Obstructive jaundice is a common presentation in several HPB cancers. Authors have commented on the injurious systemic inflammatory response, immune and myocardial suppressive effect of malignant hyperbilirubinaemia[167,168]. Others such as Junego et al, have demonstrated impaired peripheral oxygen delivery in patients with malignant biliary obstruction undergoing

pancreatoduodenectomy[142]. Published evidence on pre-operative biliary drainage for the relief of jaundice has demonstrated comparatively better post-operative outcomes compared with undrained patient cohorts[169,170]. This is an important consideration in the decision-making algorithm as the benefits that may be derived from reduction in bilirubin levels with drainage have to be weighed against the risk associated with drainage procedures. This remains a contentious area of practice within the UK with widespread variation in practice amongst HPB units. These decisions are often made on a case by case basis.

NAT remains an essential treatment adjunct in the management of colorectal cancer, CRLM and more recently pancreatic cancer[171]. Chemotherapy or combination chemoradiotherapy is often delivered over several cycles in fractions, followed by surgery. Several studies have sought to address the apparent decline in patient cardiorespiratory fitness during this period. Studies involving both oesophagogastric[172] and rectal cancer[173] patients awaiting resectional surgery, have demonstrated reduced anaerobic thresholds after NAT. Prehabilitation programmes aim to address this issue by proposing multimodal exercise-based interventions to mitigate this decline in functional capacity[174]. The role of prehabilitation as an intervention in influencing peri-operative outcomes will be addressed in detail in the SPECS trial chapter.

Understanding how these cancer and treatment-related factors influence CPET variables, allows the opportunity for more detailed patient discussions about risk and appropriate timing of CPET. It also allows for improvement of cancer care pathways by mitigating peri-operative risk through various optimisation interventions early in the diagnosis of GI cancers.

2.4.2 Risk stratification tools in major GI surgery

There exists a wide variety of risk scoring and risk prediction systems in clinical use. In general, these clinical tools are divided into ‘risk scoring’ and ‘risk prediction’ categories. Risk scoring systems assign a value or ‘weight’ to a known clinical risk factor associated with a particular outcome. An accumulation of risk factors lead to an overall increased risk. Some examples of risk scores

include Lee's Cardiac Risk Index (CRI), American Association of Anaesthesiologists Performance Score (ASA-PS) and Assess Pulmonary Risk in Surgical Patients in Catalonia (ARISCAT). Risk Prediction models (P-possum, NELA, SORT) are more dynamic and complex to compute as several patient factors are input into a multivariate model to give a risk of morbidity and mortality[175].

CRI was used within this dataset to assess risk for major non-cardiac surgery. The score gives a likelihood in percentage of a peri-operative cardiac event based on the number of factors present (**table 2.0**). Six predictive factors are considered (high risk surgery, ischaemic heart disease, a history of congestive cardiac failure, cerebrovascular disease, insulin therapy for diabetes and a serum creatinine >176μmol/L.

Table 2.0 Lees Cardiac Risk Index Factors

Points	Lee's Class	Risk (%)
0	1	0.4
1	2	0.9
2	3	6.6
>3	4	11

2.5 Aims & Objectives

To assess and clarify the relationship between ($\dot{V}O_2$peak) anaerobic threshold (AT) and ventilatory equivalent (VE/VCO_2) for carbon dioxide and outcomes in colorectal and HPB cancers. Secondly, we aimed to determine whether a particular CPET variable was a better predictor of survival in our historical patient cohort. The objective of this pre-trial analysis was to assess in a single centre and similar patient demographic cohort, whether any inherent cancer-related factors may be having an influence on CPET variables. This was deemed important in identifying confounders to inform the design and delivery of the SPECS Trial reported on in **chapter 3**.

2.6 Methods

Using a purpose-built database, we reviewed retrospectively collected CPET variables for patients having major colorectal and HPB resections from 2009-2017; this time period was selected to ensure that at least 5 years of follow-up data was available. All CPET were performed by anaesthetists trained in peri-operative techniques and certified by the Perioperative Exercise & Training Society (POETTS). The primary aim of the analysis was to determine which CPET variables ($\dot{V}O_2$ peak, AT and VE/VCO_2) were most sensitive at predicting survival in two distinct surgical populations. Patients were matched for age, sex and comorbidities. Ethical approval was attained from the HRA for use of NHS data for this purpose (**appendix 1.10**)

2.6.1 Data Collection

Data collected included patient demographics, details of neoadjuvant and adjuvant treatments, Tumour (T) stage, resection margins, number of segments resected (for CRLM), number of Lee's cardiac risk index factors (CRI), duration of hospital stay (LoS) and mortality. The primary outcome measured was survival. The secondary outcomes included length of intensive care stay and overall hospital stay and used as a proxy for complications. All non-malignant pathologies as confirmed by histology were excluded from the analysis. The data was then reviewed and validated by all the investigators before being subjected to statistical analysis.

2.6.2 Centre Selection

This retrospective cohort analysis was carried out at a single hospital in the North-West of England, East Lancashire Hospitals Trust. The centre serves as a tertiary referral site for HPB surgery and also performs complex colorectal cancer resections. The centre has a 20-year record of colorectal resection case mix comprising 35% minimally invasive (laparoscopic/laparoscopic-assisted and robotic). CPET provision has been standardised through peri-operative care pathways and through direct referral by cancer care teams for patients outside of the criteria for requiring CPET.

2.6.3 Patient selection

All selected patients had colorectal cancer confirmed on histology and either synchronous or metachronous CRLM. All patients had undergone at least one CPET prior to operative management. All patients included in the analysis had at least five years follow-up from the date of elective surgery. All CPET was performed by a team of five anaesthetists and administered in accordance with the American Thoracic Society & American College of Chest Physicians statement on CPET testing[176]. Absolute and relative contraindications as adapted from the American Thoracic Society were and adopted by POETTS were integrated into a local protocol.

2.6.4 Missing data

The 5-year survival data for patients who had CPET but did not undergo an operation for whatever reason was documented but not subjected to multivariate analysis. Where only one of the three CPET variables being assessed was recorded, this was noted but excluded from the statistical analysis. We considered applying a Monte Carlo method to provide estimates for missing data points, however decided against this to preserve the accuracy and reliability of our findings particularly as this was a small dataset. We employed this principle in instances where more than 50% of data was missing for a single variable. In those circumstances, that variable was subject to the preliminary analysis and included in the demographic data but removed from the final regression model. In our analysis this variable was $\dot{V}O_2$ peak.

2.6.5 Administration of the Test

POETTS guidelines[161] concerning the preparation and administration of the test were adhered to. During administration of the test patients were allowed to pedal continuously until maximal exertion was achieved as determined by a combination of respiratory exchange rate (RER) of >1.15, achievement of >80% of maximal heart rate (measured by 220 minus age in years) and >80% of predicted work or until required to stop on clinical grounds. Tests were performed using an Ergoline VIAsprint 150/200P cycle ergometer (Vyaire

Medical GmbH, Leibnizstrasse 7 97204, Hoechberg, Germany). Gaseous analysis was performed using the Vyaire metabolic cart Vyntus CPX & Vyntus ECG for continuous 12 lead monitoring (Vyaire Medical GmbH, Leibnizstrasse 7 97204, Hoechberg, Germany). A Nonin Xpod 3012LP PureSAT pulse oximeter (13700 1st Ave N, Plymouth, MN 55441, USA) was used for continuous oxygen saturation measurement. All tests were interpreted and reported by a consultant anaesthetist trained in perioperative techniques and certified by POETTS.

Peak oxygen consumption ($\dot{V}O_2$ peak) was determined by measuring the highest oxygen consumption in ml/min achieved within thirty seconds prior to completion of the test. The anaerobic (AT) was defined as the point at which exercising muscles started generating energy through anaerobic metabolism, which was determined using the V slope method measured in ml/kg/min. The ventilatory equivalent for carbon dioxide was determined through linear regression analysis of the minute ventilation (VE)/carbon dioxide production (VCO_2) at the anaerobic threshold.

2.6.6 Statistical Analysis

All statistical analysis was performed using GraphPad Prism 10 (GraphPad Software 2365 Northside Dr. Suite 560 San Diego, CA 92108). To control for confounding, all covariates deemed to be clinically relevant were entered into the Cox multivariate regression model to determine their influence on survival. Survival was analysed using Kaplan Meir analysis and the magnitude of effect determined using the log rank test. In some cases for uniformity, CPET variables were converted from continuous to ordinal format (**table 2.1**) Significance was defined as $p < 0.05$. A p value 0.05-0.10 was accepted as a trend. Data normality was determined by the Shapiro Wilks test and where normally distributed mean is reported; where skewed, median and interquartile range is reported.

Table 2.1 CPET Variables

CPET Variable	Continuous range	Ordinal value
AT (ml/kg/min)	7-10	low
	>11	normal
VO_2 peak (ml/kg/min)	<10	low
	10-15	moderate
	>15	normal
VE/VCO_2	26-34	normal
	>35	high

2.7 Results

Five-year follow-up data for a total of 199 (144 colorectal) and (55 CRLM) were analysed. For the colorectal cohort, 68% were male with a mean age of 70.3 (**table 2.2**). For the CRLM group 85% male with a mean age of 67 (**table 2.4**).

Table 2.2 Colorectal patient demographics

Characteristic	Total
Patient Factors	144
Mean age	70.3
Male sex	99
Risk Stratification	
Mean Number of Lee's CRI factors	0.39
CPET Variables	
Median peak oxygen consumption $\dot{V}O_2$ peak- ml/kg/min (IQR)	16.27 (7.9)
Median anaerobic threshold AT - ml/kg/min (IQR)	14.25 (5.1)
Median ventilatory equivalent for carbon dioxide VE/VCO_2 (IQR)	31 (5.0)
Surgical & Oncological Factors	
Colorectal Cancer	
T1	16
T2	18
T3	77
T4	33
Resection Margin	
R0	131
R1	13
Neoadjuvant chemo/radiotherapy	13
Adjuvant chemotherapy	55

BMI: Body Mass Index, Lee's CRI: Cardiac Risk Index factors, CPET: Cardiopulmonary Exercise Testing, IQR: Interquartile range, $\dot{V}O_2$ peak: Peak oxygen consumption, AT: anaerobic threshold, VE/VCO_2: ventilatory equivalent for carbon dioxide.

Table 2.3 Cox multivariate regression analysis for Colorectal cancers

Characteristic	Hazard Ratio	95 % CI	P value
Patient Factors			
Age	1.004	0.963 – 1.044	0.859
Male sex (female)	0.464	0.215 – 0.930	**0.038**
Risk Stratification			
Number of Lee's CRI factors	1.746	1.163 – 2.573	**0.005**
CPET Variables			
Anaerobic threshold AT- ml/kg/min - **low**	1.101	0.99 - 1.000	0.333
Ventilatory equivalent for carbon dioxide VE/VCO_2 - **High**	1.870	0.920 - 3.659	0.073
Surgical & Oncological Factors			
T Stage	1.284	0.895 – 1.894	0.189
Resection margin (R0)	0.392	0.167 – 0.998	**0.038**
Neoadjuvant chemotherapy(yes)	0.517	0.106 – 1.799	0.350
Adjuvant chemotherapy (yes)	1.478	0.794 – 2.730	0.920

BMI: Body Mass Index, Lee's CRI: Cardiac Risk Index, CPET: Cardiopulmonary Exercise Testing, AT: anaerobic threshold, VE/VCO_2 : ventilatory equivalent for carbon dioxide

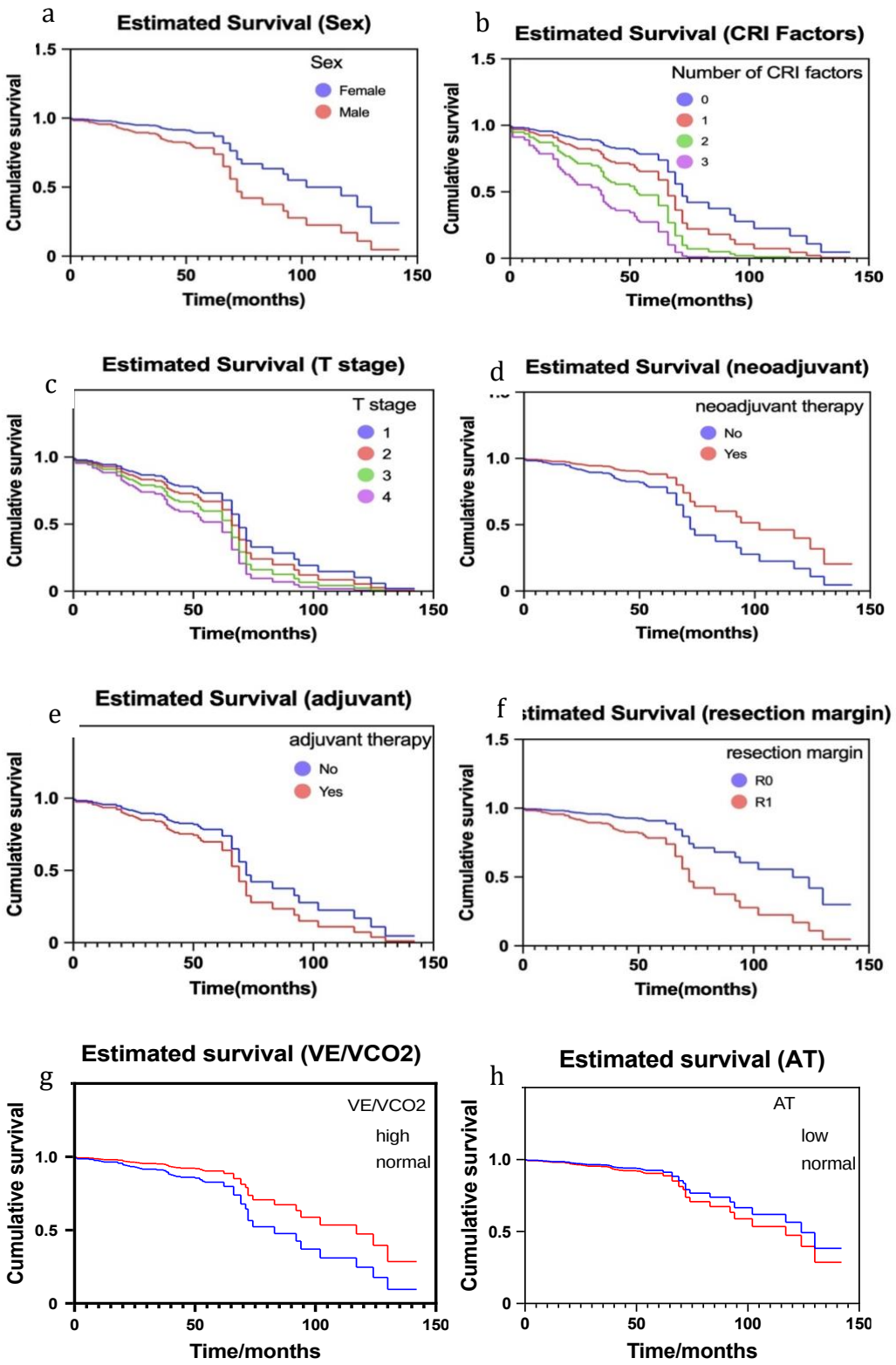


Figure 2-2. Factors associated with survival for colorectal cancer: Male sex and increasing number of CRI factors were associated with poorer survival (a &b); There was no difference in prognosis with increasing tumour size I-IV, neoadjuvant treatment or adjuvant treatment (c, d & e) respectively. A clear

resection margin (R0) was associated with better survival (f); A high ventilatory equivalent for CO2 showed a trend towards poorer survival (g); No survival difference was found between low and normal anaerobic threshold.

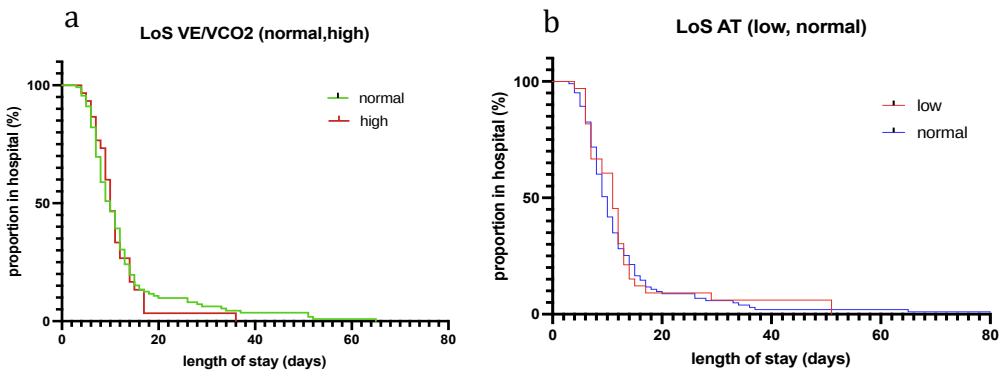


Figure 2-3. CPET variables & length of hospital stay: a- survival curves show no difference in length of hospital stay in patients with high and normal ventilatory equivalents for CO2(VE/VCO_2); b-survival curves show no difference in length of hospital stay in patients with low and normal anaerobic thresholds(AT)

2.7.1 CPET prediction of survival in colorectal cancer

In this analysis, a high VE/VCO_2 was associated with a trend towards reduced survival (HR:1.870 CI 0.920 – 3.659 p = 0.073). The strongest predictors of survival on multivariate analysis were resection margin, sex and the number of Lee's CRI factors (**figure 2-2**.). An R0 resection margin was associated with improved survival (HR: 0.392 CI 0.167 – 0.998 p = 0.038) while female sex conferred significantly better survival (HR 0.464 CI 0.215 – 0.930 p = 0.038) compared with males. An increasing number of CRI factors was associated with significantly poorer survival (HR 1.746 CI 1.163 – 2.573 p = 0.005).

There was no effect on advancing tumour stage (I-IV) and survival (HR 1.284 CI 0.895 – 1.894 p = 0.189).There was no difference in survival between those

receiving and not receiving adjuvant therapy (HR 1.478 CI 0.794 – 2.730 p = 0.920). This was also the case for neoadjuvant therapy (HR 0.517 CI 0.106 – 1.799 p = 0.350). These findings are consistent with the oncological literature concerning survival within colorectal cohorts[177].

The analysis then sought to clarify whether aerobic fitness had any influence on functional capacity hence hospital stay. Patients were compared who were at higher risk of cardiorespiratory complications (low AT, & high VE/VCO_2) with those deemed normal/low risk (normal AT & normal VE/VCO_2). There was no difference in LoS between patients in the high risk groups and low risk groups for AT (HR 0.931 CI 0.633 – 1.368 p = 0.699), and VE/VCO_2 (HR 0.939 CI 0.623 – 1.416 p = 0.742) (**figure 2-3**).

Table 2.4 HPB patient demographics: Colorectal Liver Metastases

Characteristic	Total
Patient Factors	55
Mean age	67
Male sex	46
Risk Stratification	
Mean Number of Lee's CRI	0.56
CPET Variables	
Median peak Oxygen Consumption $\dot{V}O_2$ peak-ml/kg/min (IQR)	18 (4.2)
Median anaerobic Threshold AT-ml/kg/min (IQR)	13.7(6.1)
Median Ventilatory Equivalent for Carbon dioxide VE/VCO_2 (IQR)	30 (5)
Surgical & Oncological Factors	
Median number of metastasectomies	2
Resection margin (R0)	43
Resection margin (R1)	12
Neoadjuvant chemotherapy	21
Adjuvant chemotherapy	23

BMI: Body Mass Index, Lee's CRI: Cardiac Risk Index, CPET: Cardiopulmonary Exercise Testing, IQR: Interquartile range, $\dot{V}O_2$ peak: Peak oxygen

consumption, AT: anaerobic threshold, VE/VCO_2: ventilatory equivalent for carbon dioxide.

Table 2.5 Multivariate regression analysis for Colorectal Liver Metastases (CRLM)

Characteristic	Hazard Ratio	95 % CI	P value
Patient Factors			
Mean age	1.01	0.974 - 1.064	0.431
Male sex	1.79	0.606 - 6.124	0.311
Risk Stratification			
Number of Lee's CRI	0.884	0.436 – 1.732	0.724
CPET Variables			
Anaerobic threshold (AT) ml/kg/min	1.053	0.957 – 1.159	0.281
Median ventilatory equivalent for carbon dioxide (VE/VCO_2)	1.026	0.960 – 1.089	0.424
Surgical & Oncological Factors			
Number of metastases resected	0.693	0.485 – 0.956	**0.032**
Resection margin (R0)	0.341	1.153 – 7.144	**0.019**
Neoadjuvant chemotherapy (yes)	0.581	0.239 – 1.401	0.225
Adjuvant chemotherapy (yes)	1.122	0.496 – 2.486	0.777

BMI: Body Mass Index, Lee's CRI: Cardiac Risk Index, CPET: Cardiopulmonary Exercise Testing, Peak oxygen consumption, AT: anaerobic threshold, VE/VCO_2 : ventilatory equivalent for carbon dioxide

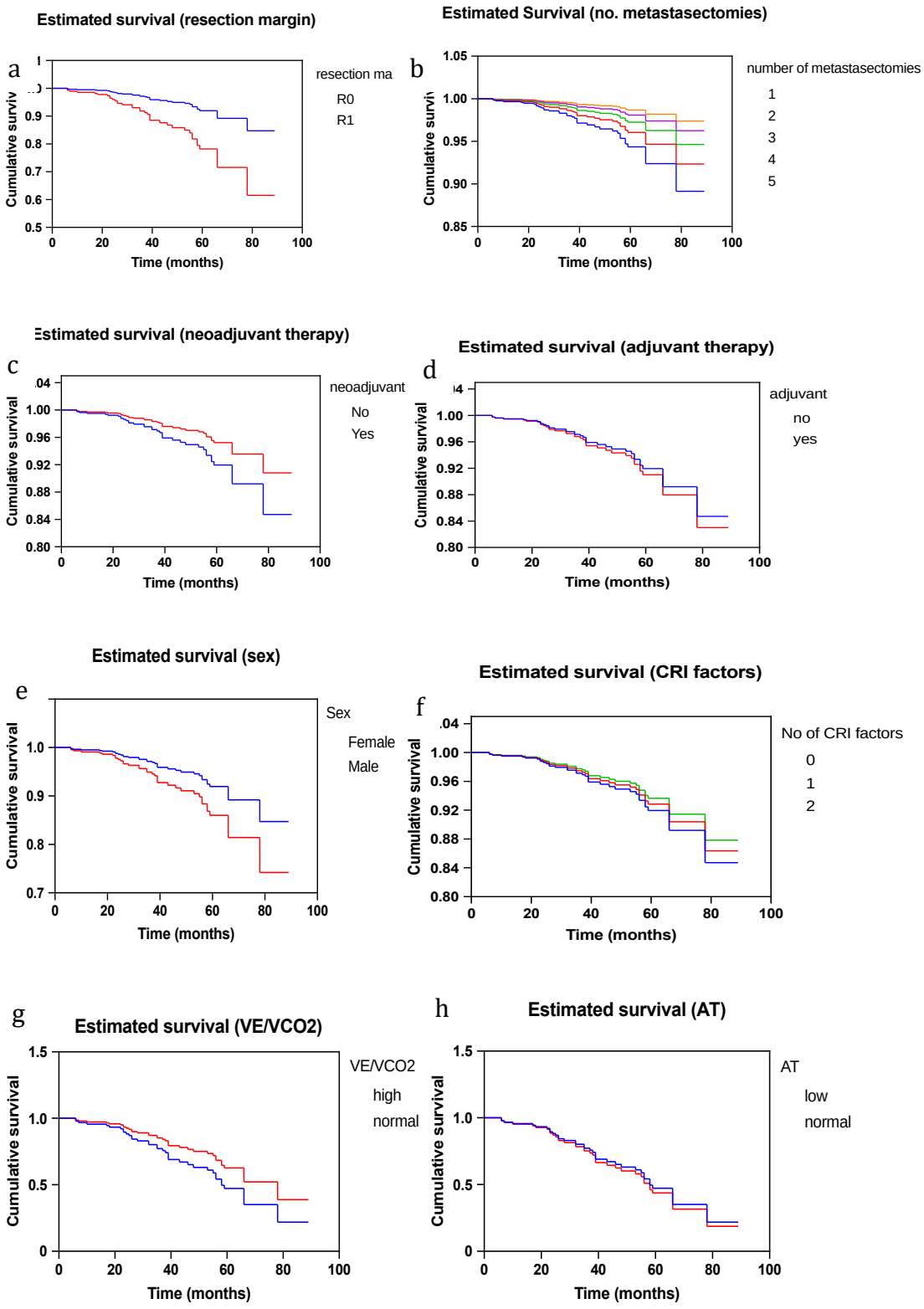


Figure 2-4. Factors associated with survival for CRLM: A clear resection margin (R0) and increasing number of metastasectomies were associated with improved survival (a&b) respectively; Neoadjuvant/adjuvant therapy, sex, CRI

factors, ventilatory equivalents for CO_2 & anaerobic (c-h) threshold were not prognostic of survival.

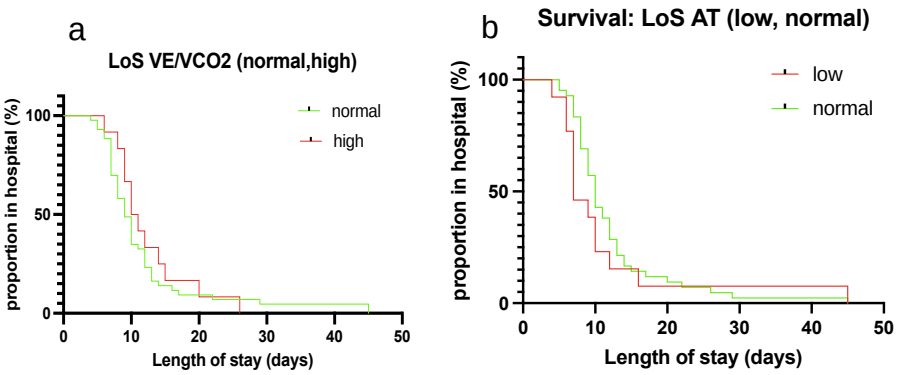


Figure 2-5. CPET variables & length of hospital stay: No effect on length of hospital stay for different thresholds of ventilatory equivalents for CO_2 (VE/VCO_2) and for anaerobic threshold (AT) (a&b)

2.7.2 CPET prediction of survival in CRLM

None of the analysed CPET variables were associated with survival. The main determinants of survival were R0 resection margin (HR 0.341 CI 1.153 – 7.144 p = 0.019) and total number of metastasectomies (HR 0.639 CI 0.485 – 0.956 p = 0.032). Interestingly, the number of metastasectomies was inversely proportional to survival. It must be noted though that only two patients underwent five metastasectomies, both of which had clear (R0) margins. It can be suggested that a clear margin was the main factor in influencing survival in this patient cohort. When length of stay was assessed in relation to CPET variables there was no association between high/normal VE/VCO_2; low/normal AT & length of hospital stay(**figure 2-5**).

2.8 Discussion

Concerning ventilatory equivalents for carbon dioxide (VE/VCO_2), for both the colorectal and CRLM cohorts our findings were consistent with previously published literature associating a high VE/VCO_2 with poorer survival in elective

oesophagogastric[136] and colorectal cancer surgery[178]. This possibly reflects the effect of chronic disorders such as chronic obstructive pulmonary disease, congestive cardiac failure that may lead to pulmonary hypertension, ventilation/perfusion mismatch and overall an inefficiency of breathing. Several studies have cited a high VE/VCO_2 as an independent predictor of mortality[179,180]. Although prior studies[181,182] have commented on the predictive value of AT in determinining peri-operative complications we found no association between AT and LoS which was used as a proxy for complications.

In our series although advancing T stage was associated with poorer median survival, the findings did not reach statistical significance. Several large studies concerning survival in colorectal cancer have shown higher T stage to strongly correlate with worse survival[177,183]. In our dataset, this finding may not have reached statistical significance. Previous studies have suggested that larger sample sizes may be required to detect this effect.

The initial postulation of this analysis was that patients classified as low/normal risk related to their CPET variables may have better functional capacity, less complications hence shorter hospital stays than their high risk counterparts. However, this was not borne out in the analysis. There may be several reasons for this observation. The categorisation used in the classification of ‘low’ and ‘high’ risk was computed from relevant published POETTS guidelines. However, it is also known that different ethic populations may have different thresholds for CPET derived variables[184], hence introducing the possibility of misclassification of ‘low’ and ‘high’ thresholds into our analysis; especially within our tertiary centre that serves a diverse ethnic population. It is also plausible that in this particular population CPET variables had no predictive value in terms of complication rates.

The strongest predictors of survival for the colorectal cancer patients were related to burden of comorbididity as evidenced by the number of CRI factors and resection margins. These observations demonstrate the interplay between oncological factors and chronic disease in influencing survival. For CRLM the number of CRI factors did not correlate with reduced survival, however

resection margin significantly determined longterm survival. Within the literature, recurrence after CRLM has been reported as high as 70%[185]. While involved resection margins may demonstrate technical failures in surgical planning or operative technique, it may also be attributable to larger lesions in more anatomically difficult regions to resect. In liver surgery it may also represent a tradeoff between achieving a clear margin with appreciable risk of postoperative liver failure and accepting an involved margin with lower risk with the option of subsequently augmenting treatment with a less invasive (ablation, chemotherapy, radiotherapy) option **(section 2.1.2 & 2.1.3**).

The retrospective nature of the data may be subject to selection bias.From the available data, it is not known what number of patients could not complete CPET. It is plausible that CPET may be correctly selecting out high risk patients who subsequently may not proceed to an operation, or have cardiopulmonary prehabilitation prior to surgery. To that end, this analysis includes CPET values at a point in time; it is not known whether patients managed to improve their aerobic capacity prior to their operation based on advice from their cancer care teams. This potential effect was not further clarified as it was beyond the scope of our analysis, and remains an area for further investigation. Studies that are designed to use CPET as an outcome measure at various time points before and after a period of physical conditioning may help elucidate this effect.

2.9 Conclusion

Our results suggest that CPET may not always be predictive of survival outcomes in colorectal and HPB cancer assessments. It is possible that the negative physiological effects of malignancy on CPET variables as mentioned in **section 2.3** may be ameliorated at least in part, once the patient is disease-free. However, our findings also highlight the importance of using CEPT alongside other clincial and physiological parameters to explain risk and gain consent. As in other studies, this analysis has again demonstrated the relationship between VE/VCO_2 and longterm survival. Prehabilitation studies have shown that supervised exercise may lead to improved cardiovascular fitness as measured by improvements in AT and $\dot{V}O_2$ peak[7,186]. This in part has

been suggested as the mechanism by which a reduction in peri-operative complications and improved functional capacity can be achieved. The SPECS trial aims to further investigate this effect in relation to 90-day outcomes.

Chapter 3: SPECS Methods

A randomised controlled trial comparing Standard care versus Prehabilitation in patients undergoing Elective hepatopancreatobiliary (HPB) and colorectal Cancer Surgery (SPECS)

3.1 Aims & Objectives

The primary aim of this trial was to investigate the biological responses to prehabilitation. This was determined by analysing the types and amounts of circulatory inflammatory cytokines and signalling proteins in blood and exercise skeletal muscle and correlating this with clinical outcomes. The secondary aim of is to investigate the cardiovascular responses to prehabilitation. This will be determined by measuring improvements in anaerobic threshold and peak oxygen consumption.

3.2 SPECS Administrative Methods

3.2.1 Patient Public Involvement (PPI)

Two separate PPIs were held to inform the design and delivery of the study. The first involved a cohort of patients who had undergone colorectal and hepatobiliary cancer surgery in the preceding 24 months. Due to pandemic restrictions this was conducted remotely. The second involved a similar patient cohort of five patients of varying physical abilities who were given the exercise programmes (**appendix 1.2a/b**) prior and asked to give comments on its difficulty and feasibility. This PPI was conducted remotely via video platform and recorded with participants consent.

3.2.2 Ethical Approval

Ethical approval was sought from the Leeds East Research Ethics Committee. Ethical approval reference 21/YH/0069 on the 21st April 2021 (**appendix 1.1**). Concurrent approval from the Health Research Authority (HRA) was received on the 26th April 2021 IRAS number 290723 (**appendix 1.3**). The study Protocol

was registered and published on the publicly available ClinicalTrials.gov website (NCT04880772).

3.2.3 Protocol

The study protocol was produced in accordance with guidelines from the Standard Protocol Items: Recommendations for Interventional Trial (SPIRIT) checklist[187] and was written using the Health Research Authority (HRA) template guide.

3.2.4 Study Compliance

The trial was conducted in compliance with the approved protocol, the Declaration of Helsinki (2013)[188], the principles of Good Clinical Practice (2016)[189], the UK Data Protection Act [190], and the UK Policy Framework for Health and Social Care Research[191].

3.2.5 Site Selection

The study was conducted at a single site at East Lancashire Hospitals NHS Trust (ELHT). This site was chosen as it provides high volume complex colorectal cancer services and serves as a tertiary referral site for hepatopancreatobiliary cancer surgery. The chief investigator (Joel Lambert) and Co-Investigator (Daren Subar) are ELHT surgeons with an established clinical working relationship with the wider research team (physiotherapy, nutrition, specialist and research nursing and pathology teams) and academic team (Coinvestigators Dr Christopher Gaffney & Dr Tom Keegan) at Lancaster University. This established collaborative network served as a pool of expertise that delivered and supported the project.

3.2.6 Study Setting

ELHT is a large integrated healthcare organization, providing high quality acute secondary healthcare for the people of East Lancashire and South Cumbria. It is a specialist center for colorectal and HPB surgical services. As a large teaching hospital, the Trust is affiliated with the University of Central Lancashire

and Lancaster University. Participants were recruited via weekly MDT meetings (colorectal and HPB) at ELHT. ELHT was the sole site, however as a regional referral centre for HPB cancers, participants were received from Lancashire Teaching Hospitals NHS Foundation Trust, University Hospitals of Morecambe Bay NHS Foundation Trust.

3.3 Participant Selection

3.3.1 Eligibility Criteria

All participants screened and deemed eligible were given a patient information sheet (PIS) (**appendix 1.4)** at the first meeting with their cancer care team. This was posted to potential participants if not available on the day. Potential participants were given a week to decide on participation and were then screened for eligibility by the CI or study nurse. Eligibility criteria were carefully decided to ensure participants were medically appropriate for selection. Participants were considered for participation once they met the inclusion criteria and none of the exclusion criteria as detailed below. Written consent was gained (**appendix 1.5**) and a letter (**appendix 1.6**) was sent to patients' General Practitioners (GP) to inform of involvement in the study.

3.3.2 Inclusion Criteria

Participant Inclusion Criteria
Aged 18-85
Sex: male/female
Radiological/tissue cancer diagnosis
Curative cancer of the colon, rectum, and major liver resection of 2 or more segments
Elective surgery (planned a minimum of 3 weeks from the date of first clinic meeting). If this minimum time limit is breached for any reason, recruited participants will be analysed on an intention to treat basis
Access to digital technology(mobile phone, tablet or laptop, home computer) to participate in supervised home exercise

3.3.3 Exclusion Criteria

Participant Exclusion Criteria
Palliative disease
Haematological malignancy
Emergency surgery
Physically unable to undergo CPET
Pregnancy
Part of any other trial with similar interventions unless previously agreed on with all CIs synchronous disease (operation on colorectal liver metastases & colorectal cancers at the same operation)
No access to digital technology(smart phone, tablet, laptop or home computer)

3.3.4 Exclusion criteria for baseline Investigations

Participants were excluded from having the below baseline investigations if they met any of these criteria, however these criteria did preclude them from participation in the study as a whole.

- DXA: Ionising radiation scanning by way of CT or PET on >10 occasions within the last year.
- CPET: Uncontrolled Atrial fibrillation, cardiac arrest in the preceding 12 months

3.4 Consort Diagram

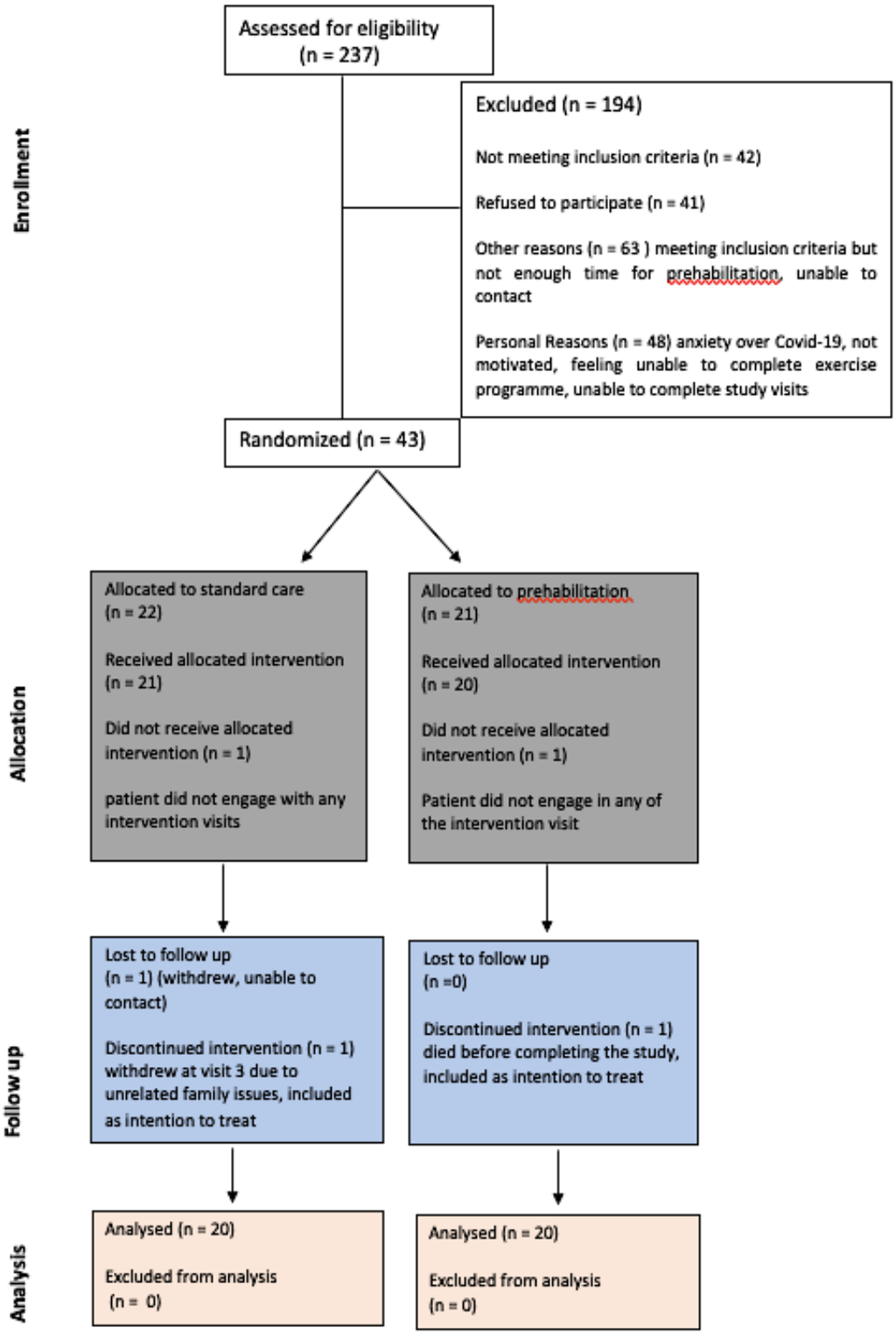


Figure 3-0 Consort Diagram

3.4.1 Sample Size

We aimed to detect the minimal clinical important difference (MCID) in VO_{2peak} at the anaerobic threshold of 1.5-2.0 ml/kg/min. Previous published data suggests that the target population has an average VO_2 max of 12 ml/kg/min. To detect a 1.5 ml/kg/min increase with a power of 0.8 and a type I error probability (0.05) we calculated that 30 participants, equally assigned to standard care (n=15) and prehabilitation (n=15) would be required. We aimed to recruit a total of 40 participants.

For circulating blood and skeletal muscle IL6 using a similar Priori power calculation with an effect size of (f) of 0.4 and an α of 0.95, a total of n=16 (8 per group) are required to detect a significant difference in IL6 levels following exercise. In order for 8 per group to finish with biopsies, we will aim to perform biopsies on 20 participants (10 per group) 50% of total study participant size. Statistically significant differences have been detected in IL6, IL1 RA, TNFα and IL1 β with a total of sixteen subjects post-exercise[192].

3.4.2 Covid-19 pandemic impact on recruitment

Ethical approval was gained during the Covid-19 pandemic. This meant that the exercise intervention that was initially planned as face to face supervised sessions at the ELHT physiotherapy gyms, had to be changed to remotely delivered sessions. The pandemic affected all aspects of recruitment, follow-up visits and general delivery of the study. Elective operating was curtailed on safety grounds and for re-allocation of resources and clinical manpower to support pandemic-related services. For significant periods CPET could not be performed as this was deemed an aerosol generating activity. Special provisions had to be made for fitting or a virus particulate filter prior to resumption of CPET. One positive aspect of delivering such an intervention during a pandemic was understanding the feasibility of remote exercise programmes and scalability of prehabilitation in general. Given finite NHS resources the author is of the view that by utilising new technologies, prehabilitation interventions can be delivered remotely and at scale.

3.4.3 Study Recruitment & Duration

Recruitment started on the date ethical approval was received, the 6th July 2021. The study concluded when the last recruited patient (13th July 2023) underwent their final CPET visit.

3.5 Intervention

3.5.1 Type of Exercise

We conducted a patient public involvement session involving previous patients who had colorectal and CRLM surgery. Patients performed two different exercise programmes (**appendix 1.2a/b)** to gauge level of difficulty and feasibility. Recruited participants to the SPECS Trial were taught how to perform exercises safely at home by the study personal trainer. For the exercise & nutrition arm details from derived CPET parameters were used to plan a moderate intensity exercise programme. A remotely supervised exercise programme was delivered by the study personal trainer. The exercise regime involved 40-min sessions of aerobic and strengthening exercise**:** to include 5min warm up, 20 min at 60-70 % VO_2 peak followed by 5 minutes cool down. Strengthening exercises focussed on core muscle groups. This was be performed after the cool down period. A single resistance band of 10kg was given to all prehabilitation participants. Alternative and equivalent exercises were employed by the personal trainer based on patient mobility factors and level of ability. These sessions were performed three times per week for a minimum of 2 weeks and a maximum of 4 weeks depending on the date for surgery. 1 session per week was monitored via a video platform by the study personal trainer. Participants were given a video of the exercises performed by the study personal trainer to be done independently for the other 2 sessions per week via the study website (**appendix 1.9**) www.surgicalbridges.co.uk/specs. All participants enrolled to the prehabilitation programme were given an exercise log to fill in (**appendix 1.7**) which was verified at the second pre-operative visit.

3.5.2 Rational for choice of moderate intensity training

Systematic reviews investigating the benefits of pre-operative exercise in elective cancer patients have shown improved cardiorespiratory fitness which correlated with improved clinical outcomes[193]. Moderate intensity exercise performed in the adjuvant setting in a group of colorectal cancer survivors showed improvements in cardiorespiratory fitness and a shift in their cytokine profiles towards a reduction in pro-inflammatory circulatory levels[194]. This molecular shift may correlate with clinically significant outcomes. Some home-based exercise programmes have shown improvements in 6MWD and an overall improvement in functional capacity[22,195]. A supervised exercise programme was proposed, as some prehabilitation studies have reported good adherence with this intervention[3,196]. While there were a few studies that have looked at nutrition as a single intervention within the context of elective cancer surgery one Canadian pilot study showed modest improvement in functional capacity with whey protein[195]. Due to the Covid 19 pandemic participants were asked to follow a home-based, remotely supervised exercise programme.

3.5.3 Habitual Activity

All participants (including standard group) habitual physical activity was measured remotely using triaxial accelerometery by GeneActiv (Activinsights, 6 Nene Road, Bicton IndustrialPark, Kimbolton, Cambs, PE28 0LF,UK). This wearable technology was worn on the wrist by participants throughout the day when active. Activity data was downloaded at the end of the intervention period (2 or 4 weeks). For the standard care group this was at the second CPET prior to surgery.

3.6 Nutrition

Participant randomised to prehabilitation underwent a 20-minute interview with a dietician to determine baseline nutritional state. At this consultation BMI was be measured and HGS recorded by the dietician. Participants underwent a nutritional blood test screen (full blood count, urea and electrolytes, glucose, liver function tests, magnesium & phosphate, calcium & albumin, clotting

function, copper, zinc, selenium, iron, ferritin, B12, folate, manganese, C-reactive protein and vitamin D). Prehabilitation participants were given a multi-vitamin (Forceval Capsules) Avonbridge House, Bath Road, Chippenham, Wilts, SN15 2BB, United Kingdom, to be taken orally for 30-day period and asked to complete food diaries for a minimum of 3 days a week for the duration of the prehabilitation period. This was originally done using NutraCheck calorie counter app, available on android and smart phone devices, however due to poor compliance this was abandoned early during the study. Compliance was checked by asking participants to bring in used capsule tabs with any used at visit 2 or on the day of surgery.

3.7 Comparator

All patients undergoing curative HPB and colorectal surgery at ELHT under a designated cancer care team were considered. Standard care involved an initial consultation with a consultant surgeon and a team of specialist nurses. Generic advice on health, nutrition and exercise was given as part of a wider Trust-wide programme called Surgery School. The prehabilitation group also had access to this service. If routine blood work revealed suboptimal haemoglobin levels or other mineral or micronutrient deficiencies, these were corrected as per Trust protocols.

3.8 Participant Journey

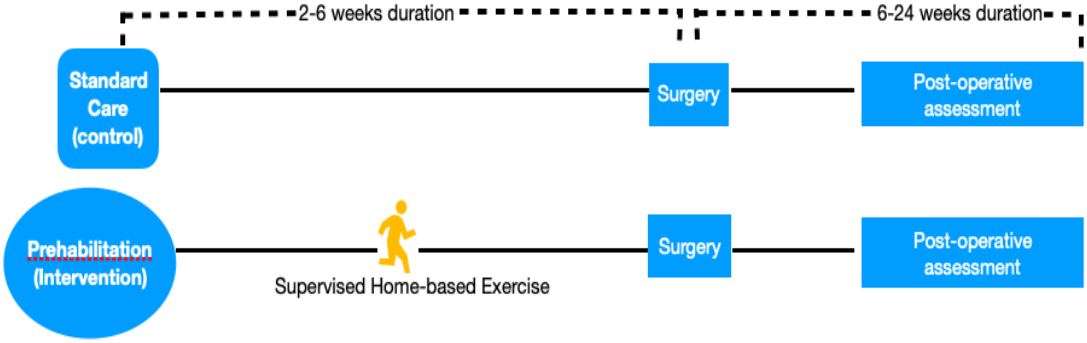


Figure 3-1 Participant Journey once randomised to standard care or prehabilitation.

3.8.1 Participant Visit Assessment

Baseline Assessment

- Standard Care Arm & Exercise/Nutrition Arm: CPET, DXA, nutrition bloods panel +/- Bx, HGS, BMI, quality of life questionnaires

Pre-operative Assessment

- Standard Care Arm & Exercise/Nutrition Arm: CPET, DXA, nutrition blood panel +/- Bx, HGS, BMI.

Post-operative Assessment

- Standard Care Arm & Exercise/Nutrition Arm: Routine ward care as per ERP guidelines, complications recorded in patient notes and by ERP team as standard as per CD

Concomitant Follow-up (6-24 weeks post-operatively)

- Standard Care Arm & Exercise/Nutrition Arm: CPET +/- Bx, repeat quality of life questionnaires

3.9 Outcomes

Primary Outcomes
Cardiopulmonary exercise Test (CPET) variables; Anaerobic threshold (AT) and VO_2 peak
Cytokines/metabolomes (IL-6, IL-10, TNF-α, IL-1 receptor antagonist) levels in blood & muscle
Secondary Outcomes
DXA-determined visceral fat/muscle ratio CD complication rates
Length of hospital stay defined as duration of stay from date of operation to discharge
30 & 90-day mortality: Defined as percentage of patients who died on or up to 30 & 90-days following date of operation respectively. These measures were chosen to capture both operative-related mortality and all-cause mortality. This was thought to be most appropriate to link the health and fitness intervention to 'all cause' outcomes[197].
Quality of life measures (QoL)Mental adjustment to Cancer Scale (MACS), Illness Perception Questionnaire (IPQ)

3.10 Randomisation

1:1 computerised block randomisation was be carried out using the 'sealed envelope' online platform A time-stamped log of the randomisation sequence was downloaded on randomisation of the last patient (**appendix 1.8).** Participants were randomised by a member of the research delivery team after their baseline CPET.

3.11 Blinding

Blinding was carried out on a pragmatic basis. Participants were randomised after CPET, consequently CPET assessors would be blinded to the subsequent randomisation. Investigators (CI & COI) and patients were not blinded to the interventions. An independent ERP team was responsible for collecting data on secondary outcomes and were not blinded to which arm participants were allocated to.

3.12 Statistical Analysis

A mixed model two-way ANOVA (time and treatment factors) was performed using Prism 6, Graphpad Software Inc., La Jolla, CA, USA. This was performed to detect differences between standard and prehabilitation groups. Statistical significance was declared at $p < 0.05$. Throughout the results analysis, median where reported was presented alongside the interquartile range(IQR); where mean values are reported they were presented alongside standard error of the mean (SEM) and 95% confidence intervals(CI). The Shapiro Wilks test was used to assess data normality and appropriate tests used as outlined above. All post hoc analyses were calculated from the effect size, means and standard deviations of the groups using G*Power software[198].

3.12.1 Data Collection

Participants were issued with a unique participant identification number (e.g SPECS001). All study encounters including consent were recorded in the patient's native hospital notes. Data were entered into a purpose-built master

database held on a secure ELHT servers. The members of the immediate research team (CI, COI, clinical research nurses and specialist nurses, ERP team) were responsible for inputting this data. Physical paper copies were also filled in a Trial Master File and stored in a designated locked cabinet in the CI office at ELHT.

Some electronic data such as length of hospital stay were automatically generated and transcribed unto the master spreadsheet. All data concerning a patient's peri-operative spell in hospital were routinely collected by the ERP team. Laboratory analysis data was be kept on secure ELHT computer servers.

Quality of life questionnaires were issued to patients at their baseline visit and asked to complete. If unable to complete on the day, they were be given pre-paid envelopes to return. The second round of questionnaires were issued to patients at their second CPET visit and asked to return via pre-paid envelopes if not able to complete on the day. Responses were collated by the enhanced recovery team on a database provided by the CI. A letter was sent out with the questionnaires indicating no obligation to complete in the event that the questionnaire caused anxiety or distress. Contact details of the CI were given in the event that participants wanted to discuss any aspect of the questionnaire.

3.13 SPECS Laboratory Methods

3.13.1 Blood sample management

Blood samples were collected using a full aseptic technique from the antecubital fossa. An 18 or 21-gauge needle connected to a 6ml BD vacutainer (BD, PL6 7BP, UK) was used. Within 2 hours of collection EDTA & Citrated samples were sent for processing at ELHT pathology laboratories for full blood count (FBC), urea and electrolytes, glucose, liver function tests, magnesium & phosphate, calcium & albumin, clotting function, copper, zinc , selenium, iron, ferritin, B12, folate, manganese, C-reactive protein and vitamin D. Some specialist analytes such as copper and zinc were measured at Central Manchester Foundation Trust Biochemistry laboratories. Within 2 hours of sample collection, one each of 6ml heparinised and citrated BD vacutainers were centrifuged at 1000

revolutions per minute (rpm) for 10 minutes at room temperature. Respectively, plasma and serum samples were micro-pipetted into 1.5 ml Eppendorf tubes (Eppendorf UK Limited, Stevenage SG1 2FP) and stored in duplicate at -80^{o}C. Samples were logged in to a purpose-built spreadsheet and signed for at every patient visit.

3.13.2 Muscle sample management

Skeletal muscle biopsies were taken from the right vastus lateralis muscle using the Bergstrom percutaneous needle biopsy technique[199]. The biopsy site was cleaned using 2% alcoholic chlorhexidine. 5-10 ml 1% lidocaine was infiltrated to the skin and then deeper to anaesthetise the fascial envelope of the muscle. A 5 mm incision was then made with a scalpel blade and muscle was sampled using a 5 mm gauge Bergström biopsy needle. 25-100 mg muscle was taken between 1-4 passes of the needle. Between patient visits, biopsies were taken a minimum of 2.5 cm apart to minimise the influence of inflammation on muscle metabolite concentrations as suggested by Constantin-Teodosiu et al[200]. The 'wet' muscle was snap frozen in liquid nitrogen within seconds of taking the sample and subsequently stored at -80^{o}C.

3.13.3 CPET Administration

CPET was administered in accordance with the protocol detailed in chapter 2.

Figure 3-2 CPET equipment setup.(A) Ergoline VIAsprint 150/200P cycle ergometer (Vyaire Medical GmbH, Leibnizstrasse 7 97204, Hoechberg, Germany). (B) Gaseous analysis Vyaire metabolic cart Vyntus CPX (Vyaire Medical GmbH, Leibnizstrasse 7 97204, Hoechberg, Germany)

3.13.4 Hand Grip Strength Measurement

A Jamar hydraulic dynamometer (3700 Sagamore Parkway North, PO Box 5729, Lafayette, IN 47903 USA) was used to measure HGS in kilograms of force. Participants were shown how to use the device prior to taking the first reading. The handles were adjusted to hand size and grip distance. After participants demonstrated that they could use the device appropriately readings were taken using both left and right hands in turn.

3.13.5 Sample Transportation

At the end of the study all samples were verified, logged out and signed for by the CI and research nurse for the study. Samples were transported frozen in dry ice to Lancaster University bioscience laboratories for analysis.

3.13.6 Sample Preparation

On the day of analysis plasma samples were allowed to thaw at room temperature (~20^{o}C).

3.13.7 Multiplex assay

3.13.7.1 Reagent (Standard) Preparation

The Biolegend Legendplex assay is a bead-based immunofluorescence technique, employing the same principles to sandwich assays. The Legendplex Multi-analyte Flow Assay kit (8999 BioLegend Way, San Diego, CA 92121 United States) was used for the analysis. The specific panel utilised was the Human Diabesity Panel (11-plex) with V-Bottom Plate.

Prior to use the lyophylised Human diabesity standard was reconstituted with 250 μL LEGENDplex Assay Buffer. This was vortexed for 30 seconds and left to stand at room temperature for 10 minutes. This was then transferred to a pre-labelled (C7) polypropylene microcentrifuge tube and used as the top standard.

3.13.7.2 Dilution of standard

Seven polypropylene tubes (C0, C1, C2, C3, C4, C5, C6) were labelled. To each tube 75 μL of Assay Buffer was added. To prepare serial 1:4 dilutions, 25 μL of C7 was added to C6 and mixed. 25 μL of C6 was then added to C5 to achieve 1:16 dilution and so on (see dilution **table 3.0** below). No standard was added to C0.

Table 3.0 Serial Dilutions for Standards

Tube/Standard	Serial Dilution	Assay Buffer to add (μL)	Standard to add (μL)	Final concentration (pmg/ml)
C7	-	-	-	10,000
C6	1:4	75	25 of C7	2,500
C5	1:16	75	25 of C6	625
C4	1:64	75	25 of C5	156.25
C3	1:256	75	25 of C4	39.01
C2	1:1024	75	25 of C3	9.77
C1	1:4096	75	25 of C2	2.44
C0	0	75	0	0

3.13.7.3 Performing assay using a V bottom plate

All reagents were allowed to equilibrate and room temperature (20-25^{o}C). For the standard wells; 25 μL of Matrix B was added to 25 μL of the pre-diluted standards described above. For the sample wells; 25 μL of Assay Buffer was added to 25 μL of the serum samples. Standards were loaded in duplicate and a record of the sample locations on the plate was made (see plate map **figure 3-3**). The pre-mixed beads were then vortexed for 30 seconds and 25 μL was added to each well on the plate. The plate was then covered with aluminium foil to protect from light and incubated on a plate shaker at 800 rpm at 20^{o}C.

	1	2	3
A	C0	C4	SPECS001 (visit 1)
B	C0	C4	SPECS001 (visit 2)
C	C1	C5	SPECS001 (visit 3)
D	C1	C5	SPECS002 (visit 1)
E	C2	C6	SPECS002 (visit 2)
F	C2	C6	SPECS002 (visit 3)
G	C3	C7	SPECS003 (visit 1)
H	C3	C7	SPECS003 (visit 2)

Figure 3-3 Plate Map Example of plate order used with standards and serum samples. Each unshaded square represents a well on the plate.

After incubation, the plate was centrifuged using a swinging bucket rotor at 1050 rpm for 5 minutes. The supernatant was then rapidly decanted into a biohazard waste container and a dry paper towel was used to blot out any remaining excess fluid with care not to disturb the beed pellet. The plate was then washed by adding 200 μL x1 wash buffer, incubated for 1 minute, then again centrifuged at 1050 rpm for 5 minutes. The decanting and drying step was repeated as prior.

To each well 25 μL of Detection Antibody was added. The plate was then sealed with a new plate sealer, covered with aluminium foil to protect from direct light and placed on a plate shaker at 800 rpm for 1 hour at room temperature. After shaking, 25 μL of streptavidin phycoerythrin (SA-PE) was added to each well directly without prior washing. A new plate sealer was applied, wrapped in aluminium foil and place on the shaker at 800 rpm for 30 minutes at room temperature. The washing and drying step above was then repeated.

The beads were the re-suspended by pipetting 150 μL of x1 Wash Buffer to each well. The plate was then read on a flow cytometer (CytoFLEX, Beckman Coulter, Brea, California). **Figure 3-4**

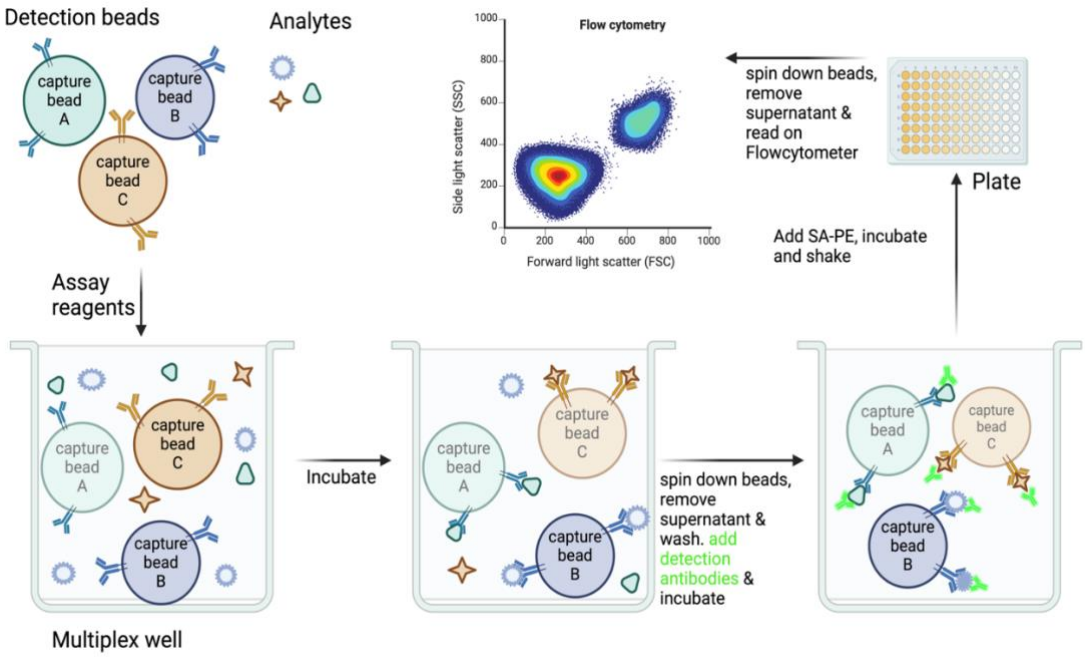


Figure 3-4 Pictorial schematic of Mutliplex assay using a V bottom plate.

3.13.7.4 Flow Cytometer Set-up

Start-up was initiated and a daily clean was carried out. The CytExpert software (CytExpert, Beckman Coulter, Brea, California United States) on the desktop was opened up and the Acquisition tab was selected to run the setup beads. To verify that beads A and B were within the pre-defined gate with a forward (FSC) and side scatter (SSC) of $>20 \times 10^4$ beads 3 was ran. The same beads 3 were used to verify that the PE fluorescence & APC fluorescence intensities were 1000-10000 & 10000 – $3x10^5$ respectively. Setup beads 2 were then ran to verify that PE fluorescence intensities of $2.4 \times 10^5 – 3 \times 10^5$ was attained for PE positive beads. A daily clean was then carried out with the setting manually switched to plate mode. Instructions for sample acquisition was then followed and data from the plate was collected and recorded. In determining that concentration of various cytokines in the samples, LEGENDplex data analysis software (Biolegend, San Diego, United States) was used. The standard curves for each analyte was then uploaded and concentrations of samples was determined by comparisons with the standard for that analyte.

3.13.7.5 Data analysis

All analysis was performed using Graphpad (GraphPad Software, Prism, California, USA). Data normality was evaluated using the Shapiro Wilks test. A 2 x 3 ANOVA was performed to compute the differences in the concentrations of circulatory cytokines at baseline, pre-operatively and post-operatively for every participant in the standard vs prehabilitation group.

3.14 SPECS DXA Scanning Methods

Weight and body mass index (BMI) was recorded at every scanning visit. Baseline scanning was performed as soon as practically possible after randomisation and CPET. This time scale had a range of 1-5 days. Pre-operative DXA was scheduled as close as possible to the date of the operation, this was 1-4 days. Post-operative scanning was done where practically possible at a point after the first post-operative visit with the parent cancer care team. This ranged between 8-16 weeks post-operatively.

The Lunar iDXA scanner (GE Healthcare, UK) was used for all scans. DXA Encore full body composition software was utilised to produce detailed reports without further interpretation by a radiographer or radiologist (**figure 3-5**). Prior to use for SPECS study patients , further machine calibration was carried out by a specially assigned GE software engineer.

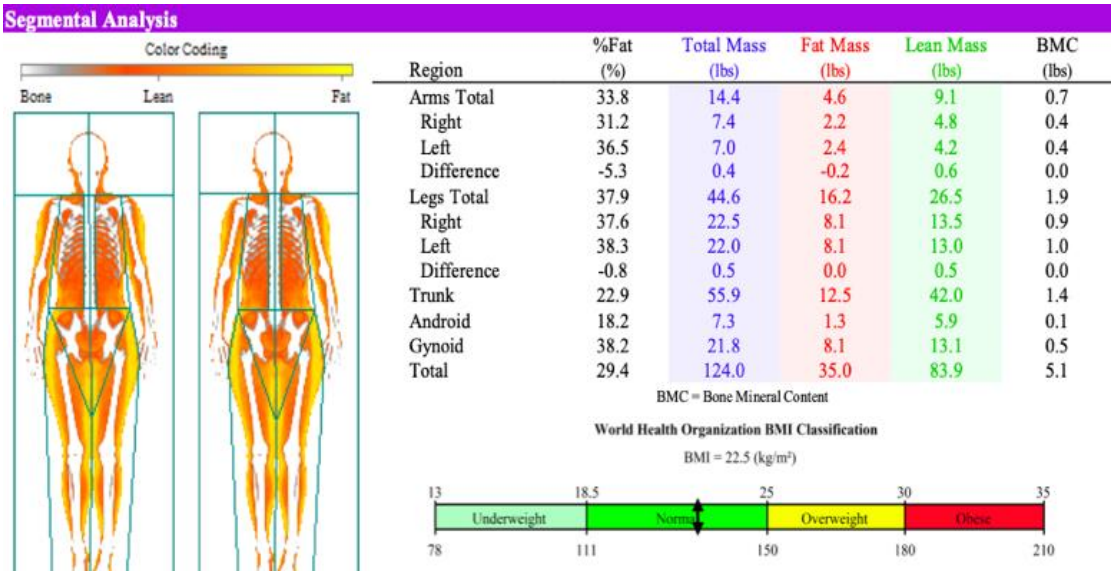


Figure 3-5 Example of DXA report by Encore software. DXA software presents detailed assessment of body composition. Distribution of fat and lean mass can also be assessed by regions (android/gynoid).

Chapter 4: The SPECS Clinical Trial: Results

A randomised controlled trial comparing **S**tandard care versus **P**rehabilitation in patients undergoing **E**lective hepatopancreatobiliary and colorectal **C**ancer **S**urgery (SPECS)

4.1 Introduction

As discussed in chapter 1, the evidence concerning the role of prehabilitation in influencing peri-operative is conflicting. The SPECS study was implemented taking into consideration the effective interventions employed in previous studies such as supervised exercise[2,6,7,22] and incorporating this into a randomised non-blinded design. Previous studies have primarily focused on assessing clinical outcomes such as length of hospital stay, complication rates, functional capacity and quality of life. This study has gone further by attempting to understand the physiological and biological changes that may underpin these observed changes in clinical outcomes. This is the first prehabilitation study to investigate the role of circulatory cytokines and signalling proteins in patients undergoing major cancer surgery. Understanding the mechanism of how biological adaptation occurs may yet offer some insight as to how we can modulate the inflammatory response to facilitate recovery. This concept of humoral and inflammatory system mediation has been a topical area within various acute settings such as intensive care, but may also have a role in elective cancer patient populations.

Some clinical measures such as length of stay may be unreliable, additionally the measurement of functional capacity by the 6-minute walk test (6MWT) as reported in previous studies; although objective, may be clinically meaningless and a crude measure of adaptation to exercise. The author of the SPECS trial has chosen CPET as a physiological outcome measure as this parameter has been well studied and corelates with outcomes such as complication rates, morbidity and mortality. Further, the SPECS trial has tried to quantify the influence of an exercise-based prehabilitation programme on body composition as measured by specialised DXA imaging. Understanding how body

composition alters may be important as evidence suggests that visceral adipose tissue has tumour-genic effects. It is also well studied that lean muscle mass has a positive effect on both recovery after major surgery and patients' physical resilience in being able to tolerate chemo/radiotherapy. With improvements in chemotherapy and new cancer treatments we may be moving into an era where some cancers can be viewed as long-term chronic illnesses. Taking that view, prehabiltation may be able to offer improved physiological and mental resilience in living with a cancer diagnosis. We aimed to understand this effect through the trial by taking a snapshot of patients' physical and psychological well-being before and after prehabilitation. These data will not be included in this thesis but will form part of a supplemental manuscript adding to the evidence base for prehabilitation.

4.2 Methods

4.2.1 Study Conduct

Ethical approval was gained from Yorkshire & the Humber Leeds East Research Ethics Committee. **REC reference 21/YH/0069 IRAS project ID 290723**. The study was conducted in accordance with the approved study Protocol. Prior to enrolment into the study potential participants were sent participant information sheets (**appendix 1.4**) and given a week to decide on participation. A member of the research team would subsequently make contact to conduct initial screening and assess for inclusion/exclusion criteria.

4.2.2 Study Duration

The study recruited its first patient on 6th July 2021 and its final patient on the 13th July 2023. The final follow-up assessments were completed on the 30th October 2023. For the colorectal cohort routine surveillance follow-up will continue for 5 years and likewise 10 year for the hepatobiliary cohort as per clinical cancer guidelines.

4.2.3 Participant journey through Trial

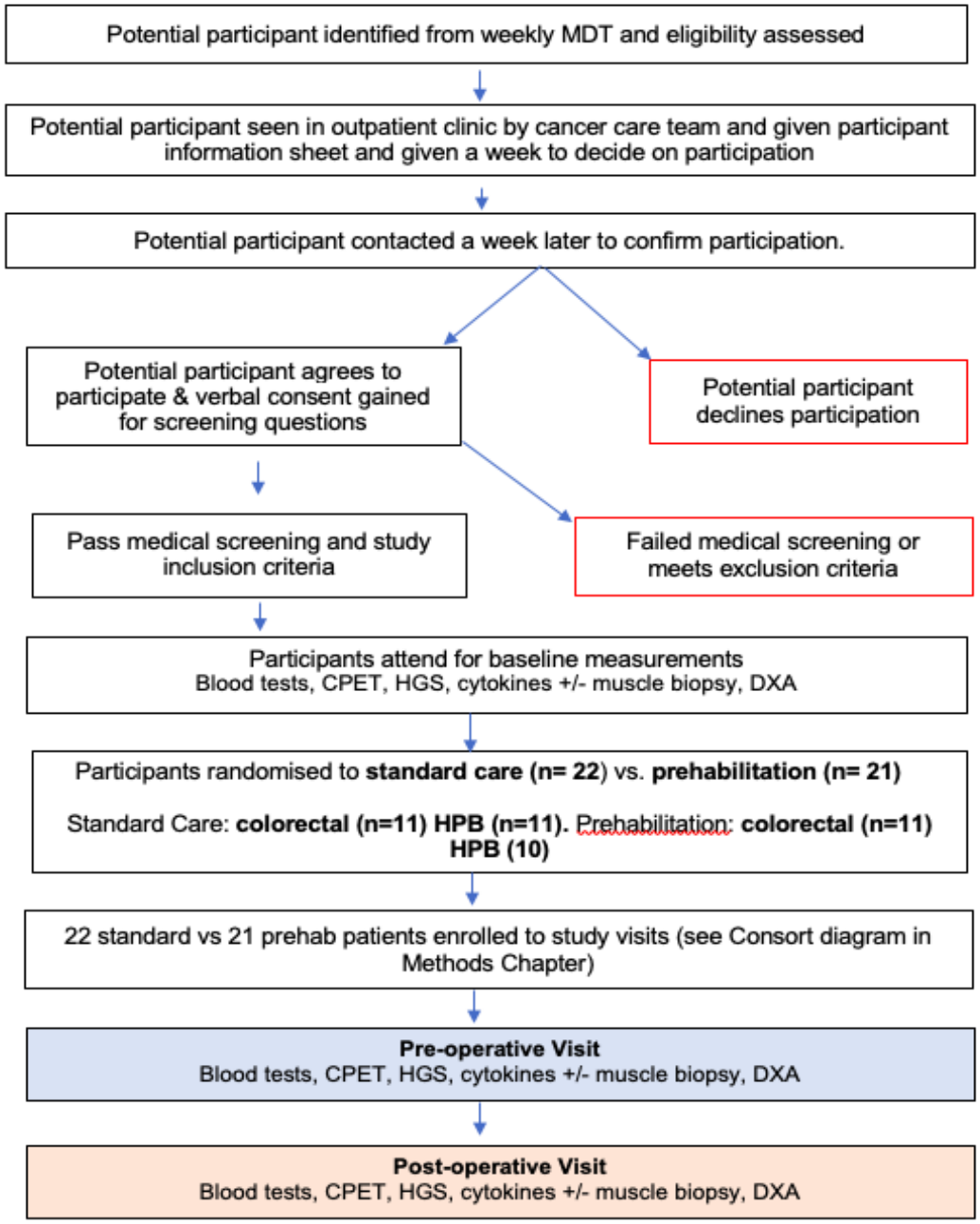


Figure 4-0 Trial Flow diagram detailing patient pathway through the SPECS Trial

4.2.4 Recruitment

As per the Consort in the General Methods **section 3.4.5**, a total of 237 patients were screened with 43 randomised after exclusions. 22 standard and 21

prehabilitation patients were enrolled in the study. The final analysis included 20 patients in the standard group and 21 patients in the prehabilitation group. One patient in the prehabilitation group unfortunately passed away before the final assessment visit, however, was included in the final analysis. The equipment and software required for DXA body composition was only procured during the midway point of recruitment. Consequently, 19 out of 41 patients (46%) had body composition measurements.

Recruitment commenced during the Covid-19 pandemic period. This meant that some higher risk patients who were eligible to be recruited were either offered alternative management strategies by their cancer care teams or declined participation due to risk of contracting Covid-19 during study visits. Conversely, fitter, lower risk patients appeared more likely and motivated to participate. This may have had the effect of introducing selection bias during the recruitment phase. A small proportion of patients although meeting inclusion criteria did not have a mobile phone or tablet to be able to participate in the remote exercise intervention and had to be excluded. We attempted to address this my providing suitable technology for the purposes of the study. However, we were only able to contract this group via post, making technology training logistically difficult within the time constraints of the study, unfortunately we were not able to overcome this barrier. This is an important consideration and may be a significant factor in patients' abilities to use and access technologies that may influence how they participate and receive healthcare and may be a contributor to health inequality.

Overall the Covid-19 pandemic had a negative impact on recruitment rates and the ability of patients to complete all study visits. Considering these unavoidable challenges the trial still managed to recruit to target and achieve favourable numbers when compared to other prehabilitation trials[2,7] of similar complexity.

4.2.5 Randomisation

Randomisation was carried out by a centralised computer-generated online service (https://www.sealedenvelope.com). This online randomisation platform

was customised to perform a simple 1:1 randomisation. The process was carried out after the baseline CPET and performed by either the PI or research nurse for the study. A time-stamped log of the randomisation can be found in **appendix 1.8**.

4.2.6 Challenges & Barriers to Recruitment

Prehabilitation programmes in general are most effective when participants have ample time to complete interventions. Exercise-based interventions require at least 2 weeks to realise biological adaptations. For the SPECS trial, stringent cancer treatment targets coupled with limited time available to enrol and deliver the prehabilitation programme presented an inherent challenge to recruitment. This was not unique to this study and have been reported in other such trials[7,17,186]

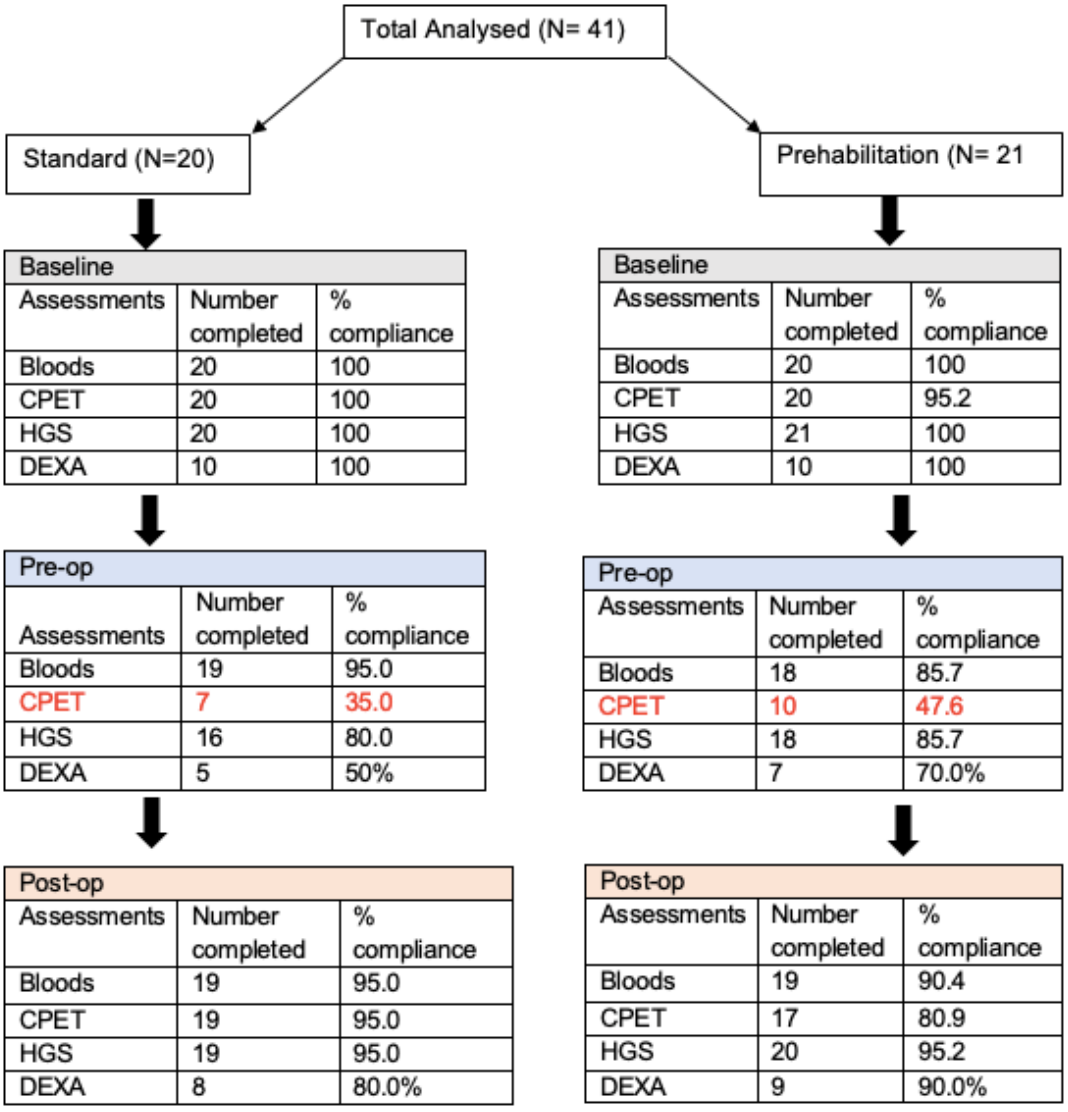
As per the Consort recruitment flowchart, out of 194 patients meeting the inclusion criteria, 63 (32%) of patients did not have enough time to complete the interventions. The reasons for this were a combination of some consultant surgeons being unaware of the study recruitment criteria and patients being fast-tracked to prevent the risk of breaching the 31-day NHS cancer target. Other challenges related to the anxiety of potential participants around being unable to complete patient visits during the pandemic. This prevailed despite assurances of universal and enhanced hospital-based safety measures. Specifically related to this, there were various national directives concerning Covid-19 vaccination with some potential participants not wanting to participate due to being unvaccinated at the time of recruitment. Additionally other potential participants were on chemotherapy regimens. This made some patients feel especially vulnerable and reduced the motivation to participate.

Barriers encountered included difficulties with travel as the recruitment site was at a tertiary centre covering a wide geographic region. The study required participants to be able to have an internet connection and a smart phone or tablet. Unfortunately, a small number of patients had to be excluded due either a lack of the technology or being unable to access or use it. This may highlight

an important wider issue about the involvement of marginalised groups in research and the wider impact of socioeconomic deprivation in the way healthcare services are used and delivered

4.2.7 Study Visit Compliance

Several factors affected the ability of the research team to deliver planned assessments at visits. Some of the technical difficulties involved a period where no CPET test could be carried out due to the risk of aerosolisation of Covid-19 viral particles during the test. This lack of CPET availability went on for three months until a viral particle filter was applied to the gaseous exchange apparatus to mitigate this risk. Another operational hurdle was finding appropriate clinical and non-clinical support staff to accommodate visits that were scheduled at short notice. The reasons for this included staff shortages and absence through illness. Other logistic factors involved cancer care teams bringing operative dates forward with inadequate time to accommodate visits. Other factors were patient related and involved concurrent illness while on chemotherapy, travel restrictions during Covid-19 pandemic and absence for other unrelated family reasons. Figure 4-1 below details the study visit and assessment compliance in each group and the reasons for missed appointments.



Baseline

Assessments	Number completed	% compliance
Bloods	20	100
CPET	20	100
HGS	20	100
DEXA	10	100

Baseline

Assessments	Number completed	% compliance
Bloods	20	100
CPET	20	95.2
HGS	21	100
DEXA	10	100

Pre-op

Assessments	Number completed	% compliance
Bloods	19	95.0
CPET	7	35.0
HGS	16	80.0
DEXA	5	50%

Pre-op

Assessments	Number completed	% compliance
Bloods	18	85.7
CPET	10	47.6
HGS	18	85.7
DEXA	7	70.0%

Post-op

Assessments	Number completed	% compliance
Bloods	19	95.0
CPET	19	95.0
HGS	19	95.0
DEXA	8	80.0%

Post-op

Assessments	Number completed	% compliance
Bloods	19	90.4
CPET	17	80.9
HGS	20	95.2
DEXA	9	90.0%

Figure 4-1 Visit and assessment compliance: Standard vs. Prehabilitation.

Both cohorts achieved high compliance for baseline assessments. The numbers completing DXA as reported above reflects the reality that body composition scanning began at the half-way point of the study due to delays in procurement and intellectual property agreements and technical issues with getting the software installed. However the high compliance reported possibly reflected the convenience and plug & play nature of the DXA scanning application. There was a considerable drop off from baseline assessments to pre-operative assessments. This was noted uniformly in both cohorts. This trend was then reversed in the post-operative period. In-particular, for pre-operative CPET measurement (highlighted in red) this decrease was

considerable in both cohorts and reflected some of the logistical challenges previously mentioned. This effect was partly addressed by applying for an amendment to increase recruitment numbers by 3 in each group to ameliorate the possible effect of underpowered data.

4.2.8 Intervention (Exercise & Nutrition) Compliance

Patients randomised to the prehabilitation arm were given a 5kg resistance band, a prescription for 30-day supply of Forceval multivitamins and an appointment with our surgical dietician at their baseline visit. Patients were also given details of the exercise programme in hard copy format and additional access to the study website with a link to the exercise page www.surgicalbridges.co.uk/specs. Patients with higher levels of ability determined by their $\dot{V}O_2$ peak were given a more challenging programme (appendix 3.1b). All prehabilitation patients completed an exercise log (appendix 1.7). This stipulated that a minimum of 2 weeks exercise (six sessions) out of which two sessions (one/week) was live with the personal trainer. Compliance was calculated by dividing the total number of sessions performed by the total number of sessions prescribed. The prehabilitation cohort achieved compliance of 98% overall which included both supervised and unsupervised sessions. The personal trainer also kept a log of supervised sessions and confirmed 100% compliance. This figure was also corroborated with data downloaded from GeneActiv accelerometry (figure 4-2) watches that were worn by patients and returned on the day of surgery. Self-reported physical exercise logs were also analysed to assess compliance. These data confirmed the intensity, duration, and frequency of active and passive exercise. Raw exercise data were extracted using GeneActiv software and mean exercise duration & intensity with standard deviation(SD) was calculated for both groups(figure 4-3).

All prehabilitation patients received a bespoke consultation from the study dietician. All Forceval packet stubs were checked on the day of surgery, which confirmed 100% compliance.

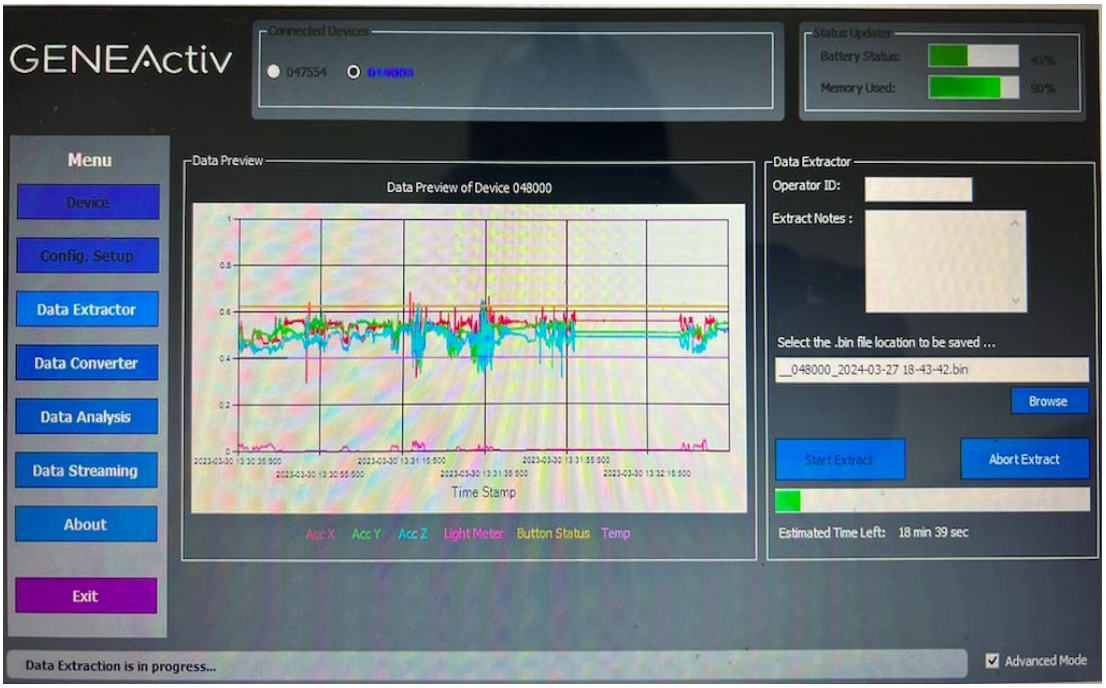


Figure 4-2. Example GeneActiv accelerometry data from study patient

Group	Mean time light(SD)	Mean time moderate (SD)	Mean time vigorous(SD)	mean daily activity time in sec(SD)
standard	8066.2(4038.7)	5606.6(3943.3)	41.7(132.1)	13714.6(7038.7)
prehabilitation	7362.6(4238.9)	5570.2(4632.9)	97.6(233.9)	13030.4(7729.3)

Figure 4-3 Accelerometry data: duration and intensity of exercise between groups

4.2.9 Statistical Analysis

4.2.9.1 Handling of raw values

As some patient data were missing at random, due to factors such as inability to schedule CPET visits, non-attendance at visits, illness and withdrawal, a mixed modelling approach was used to account for these data gaps. A mixed model two-way ANOVA (time and treatment factors; Prism 6, Graphpad Software Inc., La Jolla, CA, USA) was performed to detect differences between standard and prehabilitation groups for bloods, cytokine concentrations, CPET variables (primary endpoints) and secondary endpoints (DXA body composition and HGS). Linear mixed models were used to detect the variability of variables

examined (dependent variables) between the two different groups (standard and prehabilitation) and time points (baseline, pre-op, post-op).

Group and time point were fixed effects while individual subjects were random effects. Estimated marginal means and 95% confidence intervals (95%CI) were calculated for each mixed model. Tukey's correction was applied to account for multiple pairwise comparisons. Length of hospital stay and complications rates were subjected to Kaplan-Meier and Fishers exact test analysis respectively. Statistical significance was declared at $P<0.05$.

Throughout the results analysis, median where reported is presented alongside the interquartile range(IQR); where mean values are reported they are presented alongside standard error of the mean (SEM) and 95% confidence intervals(CI). The Shapiro Wilks test was use to assess data normality and appropriate tests used as outlined above.

4.2.9.2 Filling missing datasets

To improve statistical sensitivity Monte Carlo imputation was carried out to fill in missing values. Datasets for cytokine concentration, blood biochemistry, CPET variables and body composition were subjected to Monte Carlo imputations run at x1000 imputations to ensure data robustness and greater confidence in the accuracy the imputed values. Once missing values were imputed percentage change from baseline at pre-op and post-op were calculated and used to perform ANOVA analysis. No correction was applied for multiple pairwise comparisons. Post hoc analyses were performed using G*Power software.

4.3 Results

4.3.1 Patient Demographics

4.3.1.1 Colorectal Cohort

The details of patients in the colorectal cohort are summarised below

Table 4.0 Patient demographics for all colorectal cancer (CR) patients (standard & prehabilitation)

Characteristic		**Total**
Patient Factors		22
Median age(IQR)		67.5 (15)
Male sex		17
Risk Stratification		
ASA		
I		3
II		15
III		6
Operative Details		
Right hemicolectomy		8
Hartmanns		1
Anterior Resection		9
Abdominoperineal Resection (APR)		4
Operative Modality		
Open		2
Laparoscopic		13
Laparoscopic converted to open		4
Robotic		3
Peri-operative Factors		
Median operative time-min (IQR)		347.5 (240)
ICU admission	planned	ICU admission
	unplanned	0
Median ICU stay-days (IQR)		2 (2)
Median length of hospital stay-days (IQR)		8 (9)
90-day mortality		0
Surgical & Oncological Factors		
Tumour Staging		
Tx		3
T1		0
T2		6
T3		10
T4		3
Complications		
No complications		12
Clavien-Dindo (CD)	I	Clavien-Dindo (CD)
	II	6
	III	1
	IV	0
Neoadjuvant chemo/radiotherapy (NAC)		2
Adjuvant chemotherapy (AC)		8

AC: adjuvant chemotherapy, APR: Abdominoperineal resection, ASA: American Society of Anaesthesiologists, CD: Clavien-Dindo classification of complications, ICU: Intensive Care Unit, IQR: interquartile range, NAC: neoadjuvant chemotherapy.

4.3.1.2 Hepatobiliary Cohort

Details of patients in the hepatobiliary cohort are summarised below

Table 4.1 Patient demographics for all hepatobiliary (HB) patients (standard & prehabilitation)

Characteristic		Total
Patient Factors		19
Median age(IQR)		63(17)
Male sex		14
Risk Stratification		
ASA		
I		2
II		13
III		4
Pathology		
Colorectal Liver Metastases (CRLM)		14
Hepatocellular carcinoma (HCC)		3
Adenoma		2
Operative Details		
Major liver resection		17
Minor liver resection		2
Operative Modality		
Open		0
Laparoscopic		11
Laparoscopic converted to open		7
Robotic		1
Peri-operative Factors		
Median operative time-min (IQR)		360 (310)
ICU admission	Planned	19
	unplanned	0
Median ICU stay-days (IQR)		2 (2)
Median length of hospital stay-days(IQR)		6 (5)
90-day mortality		0
Oncological Factors		
Li-Rads Staging		
I		0
II		0
III		2
IV		0
V		3
Complications		
No complications		13
Clavien-Dindo(CD)	I	0
	II	2
	III	3
	IV	1
Neoadjuvant chemo/radiotherapy (NAC)		12
Adjuvant chemotherapy (AC)		9

ASA: American Society of Anaesthesiologists, ICU: Intensive Care Unit, CD: Clavien-Dindo classification of complications, ICU: Intensive Care Unit, IQR: interquartile range, Lirads: Liver image reporting & data systems, NAC: neoadjuvant chemotherapy

4.3.1.3 Composition of patients within the groups

Details of the individual patient cohort compositions between the colorectal and hepatobiliary groups are summarised below.

Table 4.3 Cohort composition of groups

No	Age	Group	Cohort	TNM /LiRad stage		Age	Group	Cohort	TNM/LiRad stage
1	65	standard	CR	T3aN0M0		63	prehab	HB	CRLM
2	59	standard	CR	T2N0M0		65	prehab	CR	T1N0M0
3	41	standard	HB	LR5 HCC		68	prehab	HB	LR3 HCC
4	59	standard	CR	T2N1M0		73	prehab	CR	T4N1M0
5	47	standard	CR	T4N2M0		64	prehab	HB	T3bN1M1
6	77	standard	CR	T2NxMx		74	prehab	HB	CRLM
7	67	standard	CR	T4aN0M0		68	prehab	CR	T3N0M0
8	55	standard	HB	T3 N0 R0		54	prehab	HB	LR5 HCC
9	82	standard	HB	LR5 HCC		75	prehab	CR	T3N0M0
10	49	standard	HB	T4N2M1		57	prehab	CR	T2N2M0
11	63	standard	HB	T3N0M1		73	prehab	CR	T3aN1aM0
12	28	standard	HB	T4aN1bM1		75	prehab	CR	T3/4 N0M0
13	69	Standard	HB	T4N2M1		64	prehab	HB	CRLM
14	61	standard	CR	T3N1M0		51	prehab	HB	LR3 HCC
15	74	standard	CR	T3N0M0		61	prehab	HB	T3N02M0
16	83	standard	CR	T3N0M1		78	prehab	CR	T3N1M0
17	74	standard	CR	TXN0M0		60	prehab	CR	TxN0M0
18	68	standard	HB	T4N2M0		67	prehab	CR	T2/3N0M0
19	64	standard	HB	T2/3N1M0		65	prehab	HB	T3N1M1
20	78	standard	CR	T2N0M0		63	prehab	HB	CRLM
21						65	prehab	CR	T1N0M0

CR: colorectal, HB: hepatobiliary, HCC: hepatocellular carcinoma, TNM: tumour node metastases, LiRad: Liver image reporting & data systems

The proportion of colorectal and hepatobiliary patients was spread evenly across the groups (Standard: 11(55%) CR & 9(45%) HB; Prehab: 11(52%) CR & 10(48%) HB). The rationale behind including both colorectal and hepatobiliary cohorts within a single grouping was based on the recognition of both colorectal and CRLM as a homogenous population, hence with similar demographic characteristics.

4.3.1.4 Demographic differences between Groups (Standard vs. Prehabilitation) measured at baseline

Details of baseline demographic between the groups are summarised below. There was no statistical difference in demographic characteristics.

Table 4.3 Differences in baseline characteristics of cohorts

Demographic characteristics		Standard	Prehabilitation	P value
Median Age (IQR)		64.5(17)	65(11)	0.722
Sex	male	14	17	0.4841
	female	6	4	
Median ASA (IQR)		2(0)	2(1)	0.561
Median BMI (IQR)		29.03 (9.47)	29.55 (7.08)	0.763

ASA: American Society of Anaesthesiologists, BMI: body mass index (kg/m^2), IQR: interquartile range

4.3.2 Comparison of cytokine & signalling protein mean concentrations changes in standard care vs prehabilitation

The tables below summarise the percentage change from baseline in cytokine and signalling protein concentrations between the groups. Trends are highlighted in **bold** and statistically significant measures highlighted in red.

Table 4.4 Percentage change from baseline to pre-op of cytokine & signalling protein concentrations (standard vs. prehabilitation)

Cytokine/ Signalling protein	mean % change from baseline Standard vs. Prehabilitation Pre-op	95% CI	P value
PAI-1	648.4	-27.24 to 1324	**0.0597**
GLP-1(Total)	132.2	-32.97 to 297.3	0.1151
Insulin	-297.7	-611.8 to 16.41	**0.0629**
C-Peptide	-3.881	-72.40 to 64.64	0.9105
TNF-α	65.85	-126.3 to 258.0	0.4971
Glucagon	-59.84	-181.7 to 62.03	0.3313
Leptin	3526	-557.8 to 7611	**0.0896**
Cortisol	-757.9	-1787 to 271.7	0.1468
IL-1β	-93.10	-208.3 to 22.11	0.1117
IL-6	-100.8	-329.9 to 128.3	0.3837
GLP-1 (Active)	-35.70	-332.8 to 261.4	0.8116

PAI-1: plasminogen activator inhibitor-1, GLP-1: glucagon-like peptide-1 TNF-α: tumour necrosis factor-alpha, IL-1β: interleukin-1 beta, IL-6:interleukin-6, CI: confidence interval, p value: probability value.

Table 4.5 Percentage change from baseline to postop of cytokine & signalling protein concentrations (standard vs. prehabilitation)

Cytokine/ Signalling protein	mean % change from baseline Standard vs. Prehabilitation Post-op	95% CI	P value
PAI-1	302.9	-372.7 to 978.5	0.3749
GLP-1(Total)	61.81	-103.3 to 227.0	0.4585
Insulin	-195.8	-509.9 to 118.3	0.2183
C-Peptide	66.57	-1.949 to 135.1	**0.0567**
TNF-α	4.613	-187.5 to 196.8	0.9620
Glucagon	-69.12	-191.0 to 52.75	0.2623
Leptin	-2249	-6334 to 1835	0.2763
Cortisol	-247.1	-1277 to 782.4	0.6341
IL-1β	-63.75	-179.0 to 51.47	0.2741
IL-6	-48.32	-277.4 to 180.8	0.6757
GLP-1 (Active)	167.2	-129.9 to 464.3	0.2659

PAI-1: plasminogen activator inhibitor-1, GLP-1: glucagon-like peptide-1 TNF-α: tumour necrosis factor-alpha, IL-1β: interleukin-1 beta, IL-6:interleukin-6, CI: confidence interval, p value: probability value

Table 4.6 Comparison of % change from baseline between pre-op & post-op in the standard and prehabilitation group.

Cytokine/ Signalling protein	mean % change from baseline Standard Pre-op vs. Post-op (95% CI)	P value		mean % change from baseline Prehabilitation Pre-op vs. Post-op (95% CI)	P value
PAI-1	397.6 (8.539 to 786.7)	**0.0454**		52.12 (-327.6 to 431.8)	0.7828
GLP-1(Total)	34.87 (-104.2 to 173.9)	0.6148		-35.51 (-171.2 to 100.2)	0.5996
Insulin	-100.0 (-232.1 to 32.00)	0.1335		1.858 (-127.0 to 130.7)	0.9769
C-Peptide	-72.05 (-130.0 to -14.12)	**0.0161**		-1.592 (-58.12 to 54.94)	0.9549
TNF-α	54.95 -10.49 to 120.4	**0.0974**		-6.284 (-70.15 to 57.58)	0.8433
Glucagon	-7.198 (-77.91 to 63.52)	0.8379		-16.48 (-85.49 to 52.53)	0.6317
Leptin	4744 (656.1 to 8833)	**0.0241**		-1031 (-5021 to 2958)	0.6040
Cortisol	-60.16 (-1099 to 978.9)	0.9074		450.6) (-563.4 to 1465	0.3743
IL-1β	-30.98 (-106.4 to 44.42)	0.4110		-1.622 (-75.21 to 71.96)	0.9647
IL-6	36.24 (-126.3 to 198.8)	0.6546		88.73 (-69.93 to 247.4)	0.2649
GLP-1 (Active)	-10.58 (-240.1 to 218.9)	0.9262		192.3 (-31.61 to 416.3)	**0.0902**

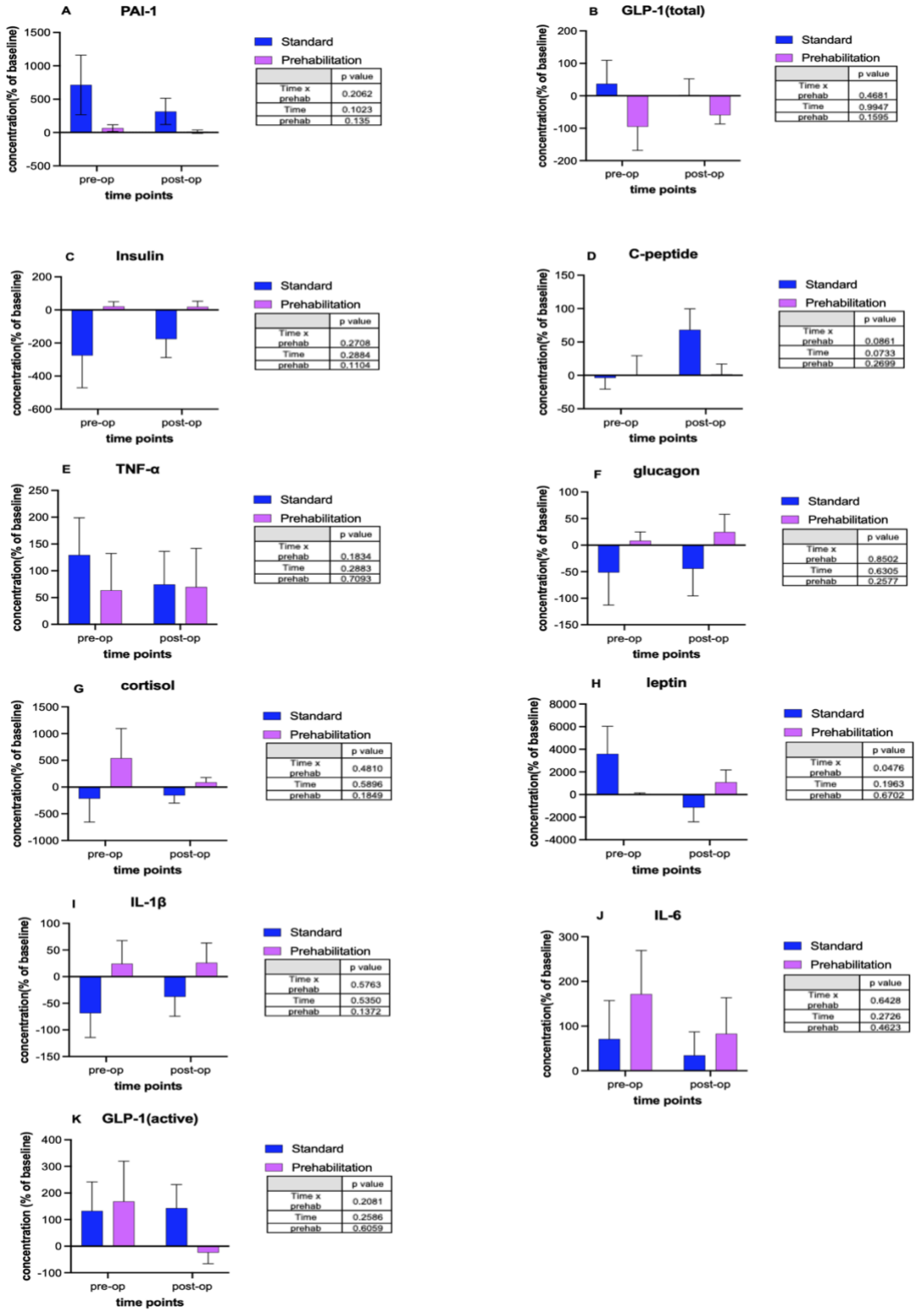


Figure 4-4 Multi-comparison ANOVA analysis

4.3.3 Comparison of blood biochemistry mean values changes in standard care vs prehabilitation.

The tables below summarise the percentage change from baseline in blood biochemistry between the groups.

Table 4.7 Percentage change from baseline to pre-op of blood biochemistry (standard vs. prehabilitation)

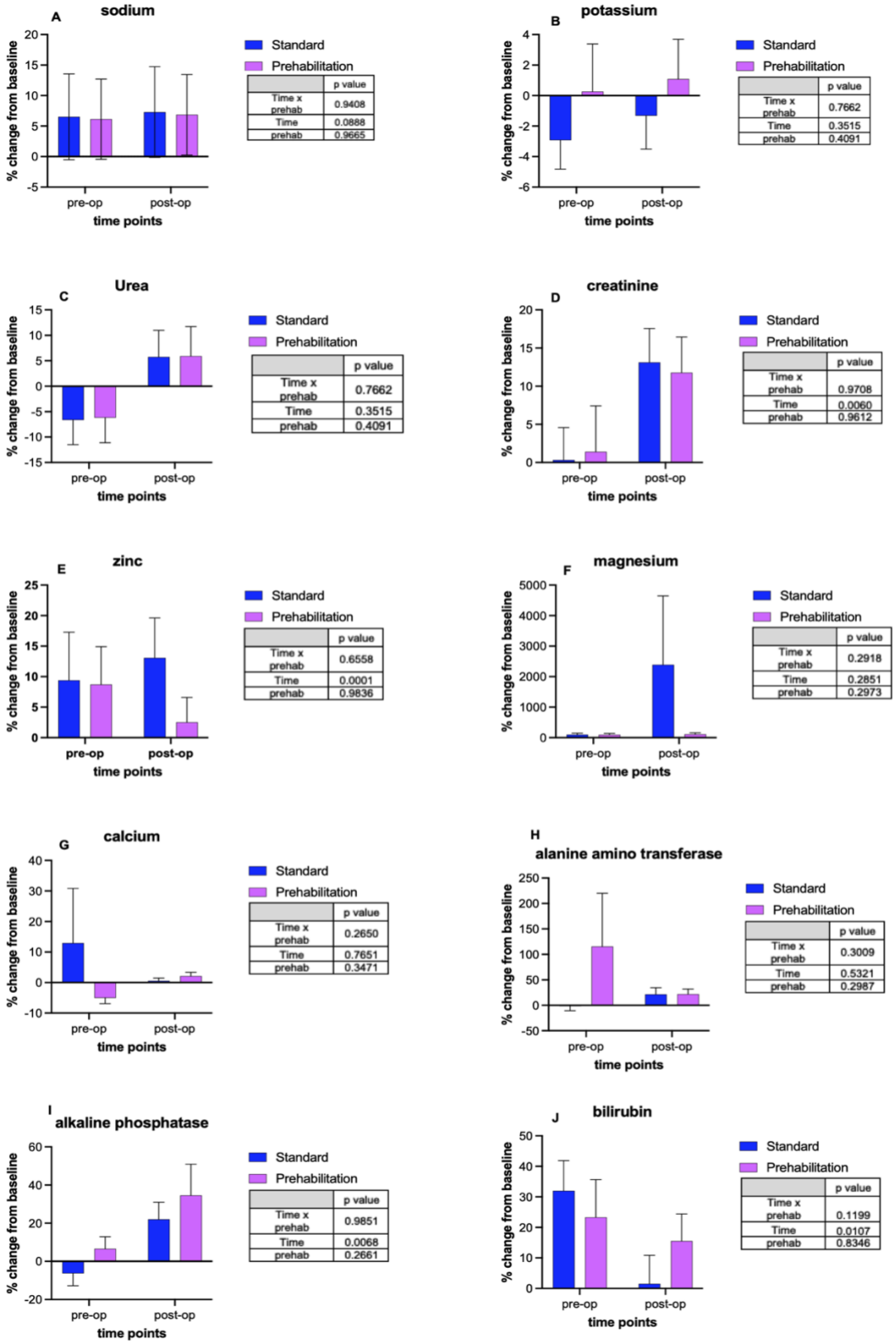
Bloods	mean % change from baseline Standard vs. Prehabilitation Pre-op	95 % CI	P value
sodium	0.3799	-19.06 to 19.82	0.9691
potassium	-3.184	-10.34 to 3.968	0.3780
urea	-0.4545	-15.23 to 14.32	0.9513
creatinine	-1.088	-15.03 to 12.85	0.8769
zinc	0.6958	-16.88 to 18.27	0.9373
magnesium	4.524	-3012 to 3021	0.9976
calcium	17.94	-6.308 to 42.19	0.1447
Alanine amino transferase	-117.4	-274.7 to 39.87	0.1412
Alkaline phosphatase	-12.92	-42.72 to 16.88	0.3905
bilirubin	8.667	-20.27 to 37.60	0.5526
albumin	-3.466	-13.75 to 6.815	0.5039
B12	-5.155	-64.50 to 54.19	0.8631
iron	-7.006	-41.62 to 27.61	0.6880
copper	-7.952	-18.00 to 2.099	0.1192
phosphate	2.489	-17.69 to 22.66	0.8065
ferritin	69.64	-96.16 to 235.4	0.4055
folate	-142.2	-296.5 to 12.17	**0.0705**
C-reactive protein	10.58	-62.80 to 83.96	0.7747
haemoglobin	-0.1309	-20.61 to 20.35	0.9899
White cell count	-17.40	-38.79 to 3.987	0.1093

Table 4.8 Percentage change from baseline to post-op of blood biochemistry(standard vs. prehabilitation

Bloods	mean % change from baseline Standard vs. Prehabilitation Post-op	95 % CI	P value
sodium	0.4438	-18.99 to 19.88	0.9639
potassium	-2.413	-9.565 to 4.738	0.5036
urea	-0.1443	-14.92 to 14.63	0.9845
creatinine	1.355	-12.58 to 15.29	0.8470
zinc	10.55	-7.017 to 28.13	0.2353
magnesium	2276	-740.1 to 5293	0.1370
calcium	-1.603	-25.85 to 22.65	0.8956
Alanine amino transferase	-0.4227	-157.7 to 156.8	0.9957
Alkaline phosphatase	-12.55	-42.35 to 17.25	0.4041
bilirubin	-13.99	-42.93 to 14.94	0.3386
albumin	-4.454	-14.73 to 5.828	0.3910
B12	-0.8668	-60.21 to 58.48	0.9769
iron	-1.718	-36.33 to 32.89	0.9215
copper	-0.2761	-10.33 to 9.775	0.9565
phosphate	-8.087	-28.26 to 12.09	0.4272
ferritin	137.6	-28.21 to 303.4	0.1025
folate	-39.69	-194.0 to 114.6	0.6100
C-reactive protein	26.56	-46.82 to 99.94	0.4731
haemoglobin	-1.656	-22.14 to 18.83	0.8725
White cell count	4.492	-16.90 to 25.88	0.6769

Table 4.9 Comparison of % change from baseline between pre-op & post-op in the standard and prehabilitation group.

Bloods	mean % change from baseline	P value		mean % change from baseline	P value
	Standard			**Prehabilitation**	
	Pre-op vs. Post-op (95% CI)			Pre-op vs. Post-op (95% CI)	
sodium	-0.7777 (-2.030 to 0.4749)	0.2165		-0.7139 (-1.905 to 0.4776)	0.2327
potassium	-1.598 (-5.372 to 2.175)	0.3965		-0.8279 (-4.417 to 2.761)	0.6432
urea	-12.40 (-24.74 to -0.06475)	**0.0489**		-12.09 (-23.83 to -0.3568)	**0.0437**
creatinine	-12.80 (-20.78 to -4.825)	**0.0024**		-10.36 (-17.94 to -2.771)	**0.0088**
zinc	-3.661 (-18.81 to 11.49)	0.6276		6.198 (-8.216 to 20.61)	0.3895
magnesium	-2288 (-5406 to 829.4)	0.1456		-16.23 (-2982 to 2949)	0.9912
calcium	12.37 (-12.97 to 37.71)	0.3292		-7.173 (-31.27 to 16.93)	0.5504
Alanine amino transferase	-23.33 (-186.9 to 140.3)	0.7744		93.65 (-61.95 to 249.2)	0.2306
Alkaline phosphatase	-28.31 (-57.12 to 0.5070)	**0.0540**		-27.94 (-55.35 to -0.5304)	**0.0459**
bilirubin	30.46 (9.568 to 51.34)	**0.0054**		7.798 (-12.07 to 27.67)	0.4318
albumin	-13.09 (-20.83 to -5.348)	**0.0015**		-14.08 (-21.44 to -6.713)	**0.0004**
B12	-7.718 (-29.61 to 14.17)	0.4798		-3.430 (-24.25 to 17.39)	0.7407
iron	-3.574 (-33.82 to 26.67)	0.8122		1.713 (-27.05 to 30.48)	0.9047
copper	-11.65 (-18.91 to -4.390)	**0.0024**		-3.974 (-10.88 to 2.932)	0.2513
phosphate	0.02763 (-17.60 to 17.66)	0.9975		-10.55 (-27.32 to 6.222)	0.2106
ferritin	-59.82 (-217.6 to 97.98)	0.4476		8.129 (-142.0 to 158.2)	0.9133
folate	7.631 (-154.8 to 170.1)	0.9248		110.1 (-44.44 to 264.6)	0.1574
C-reactive protein	-4.338 (-65.92 to 57.24)	0.8873		11.64 (-46.93 to 70.22)	0.6896
haemoglobin	-4.812 (-10.99 to 1.361)	0.1229		-6.338 (-12.21 to -0.4654)	**0.0351**
White cell count	-9.258 (-30.13 to 11.62)	0.3750		12.63 (-7.222 to 32.49)	0.2055


A
sodium
% change from baseline
time points
pre-op
post-op
Standard
Prehabilitation
p value
Time x prehab 0.9408
Time 0.0888
prehab 0.9665
B
potassium
Time x prehab 0.7662
Time 0.3515
prehab 0.4091
C
Urea
Time x prehab 0.7662
Time 0.3515
prehab 0.4091
D
creatinine
Time x prehab 0.9708
Time 0.0060
prehab 0.9612
E
zinc
Time x prehab 0.6558
Time 0.0001
prehab 0.9836
F
magnesium
Time x prehab 0.2918
Time 0.2851
prehab 0.2973
G
calcium
Time x prehab 0.2650
Time 0.7651
prehab 0.3471
H
alanine amino transferase
Time x prehab 0.3009
Time 0.5321
prehab 0.2987
I
alkaline phosphatase
Time x prehab 0.9851
Time 0.0068
prehab 0.2661
J
bilirubin
Time x prehab 0.1199
Time 0.0107
prehab 0.8346

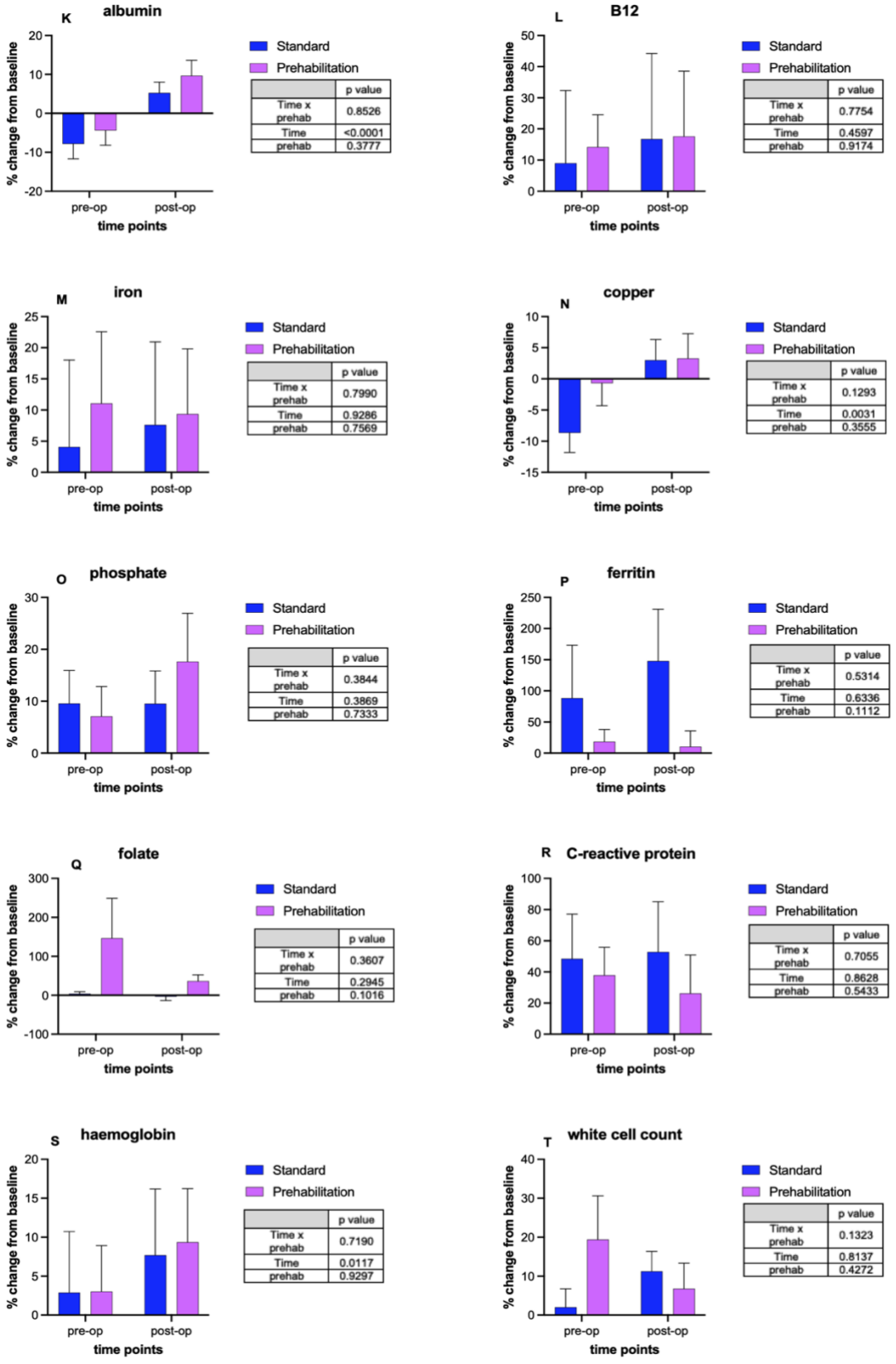


Figure 4-5 Multi-comparison ANOVA for blood biochemistry

4.3.4 Comparison of CPET variables in the standard vs. prehabilitation group

The tables below summarise the changes in CEPT variables from baseline between the groups.

Table 4.10 Mean percentage change in CPET variables from baseline to pre-op (standard vs. prehabilitation)

CPET Variable	mean % change from baseline Standard vs. Prehabilitation **Pre-op**	95 % CI	P value
Peak oxygen consumption $\dot{V}O_2$ peak-ml/kg/min	-6.841	-19.30 to 5.615	0.2774
Anaerobic threshold AT -ml/kg/min	-14.93	-31.93 to 2.066	**0.0842**
Ventilatory equivalent for carbon dioxide VE/VCO_2	26.39	-10.75 to 63.53	0.1611

CI: Confidence Interval, CPET: Cardiopulmonary Exercise Testing, $\dot{V}O_2$ peak: peak oxygen consumption, AT: anaerobic threshold, VE/VCO_2: ventilatory equivalent for carbon dioxide, p value: probability value

Table 4.11 Mean percentage change in CPET variables from baseline to post-op (standard vs. prehabilitation)

CPET Variable	mean % change from baseline Standard vs. Prehabilitation **Post-op**	95 % CI	P value
Peak oxygen consumption $\dot{V}O_2$ peak-ml/kg/min	-3.970	-16.43 to 8.486	0.5274
Anaerobic threshold AT -ml/kg/min	1.825	-15.17 to 18.82	0.8311
Ventilatory equivalent for carbon dioxide VE/VCO_2	25.55	-11.59 to 62.69	0.1746

CI: Confidence Interval, CPET: Cardiopulmonary Exercise Testing, $\dot{V}O_2$ peak: peak oxygen consumption, AT: anaerobic threshold, VE/VCO_2: ventilatory equivalent for carbon dioxide, p value: probability value.

Table 4.12 Comparison of % change from baseline between pre-op & post-op in the standard and prehabilitation group.

CPET Variable	mean % change from baseline	P value		mean % change from baseline	P value
	Standard			**Prehabilitation**	
	Pre-op vs. Post-op (95% CI)			Pre-op vs. Post-op (95% CI)	
Peak oxygen consumption $\dot{V}O_2$ peak-ml/kg/min	2.024 (-7.037 to 11.08)	0.6535		4.895 (-3.936 to 13.73)	0.2686
Anaerobic threshold AT - ml/kg/min	-0.2299 (-11.89 to 11.43)	0.9684		16.53 (5.156 to 27.90)	**0.0056**
Ventilatory equivalent for carbon dioxide VE/VCO_2	-17.33 (-50.38 to 15.72)	0.2949		-18.17 (-50.38 to 14.04)	0.2604

CI: Confidence Interval, CPET: Cardiopulmonary Exercise Testing, $\dot{V}O_2$ peak: peak oxygen consumption, AT: anaerobic threshold, VE/VCO_2: ventilatory equivalent for carbon dioxide, p value: probability value.

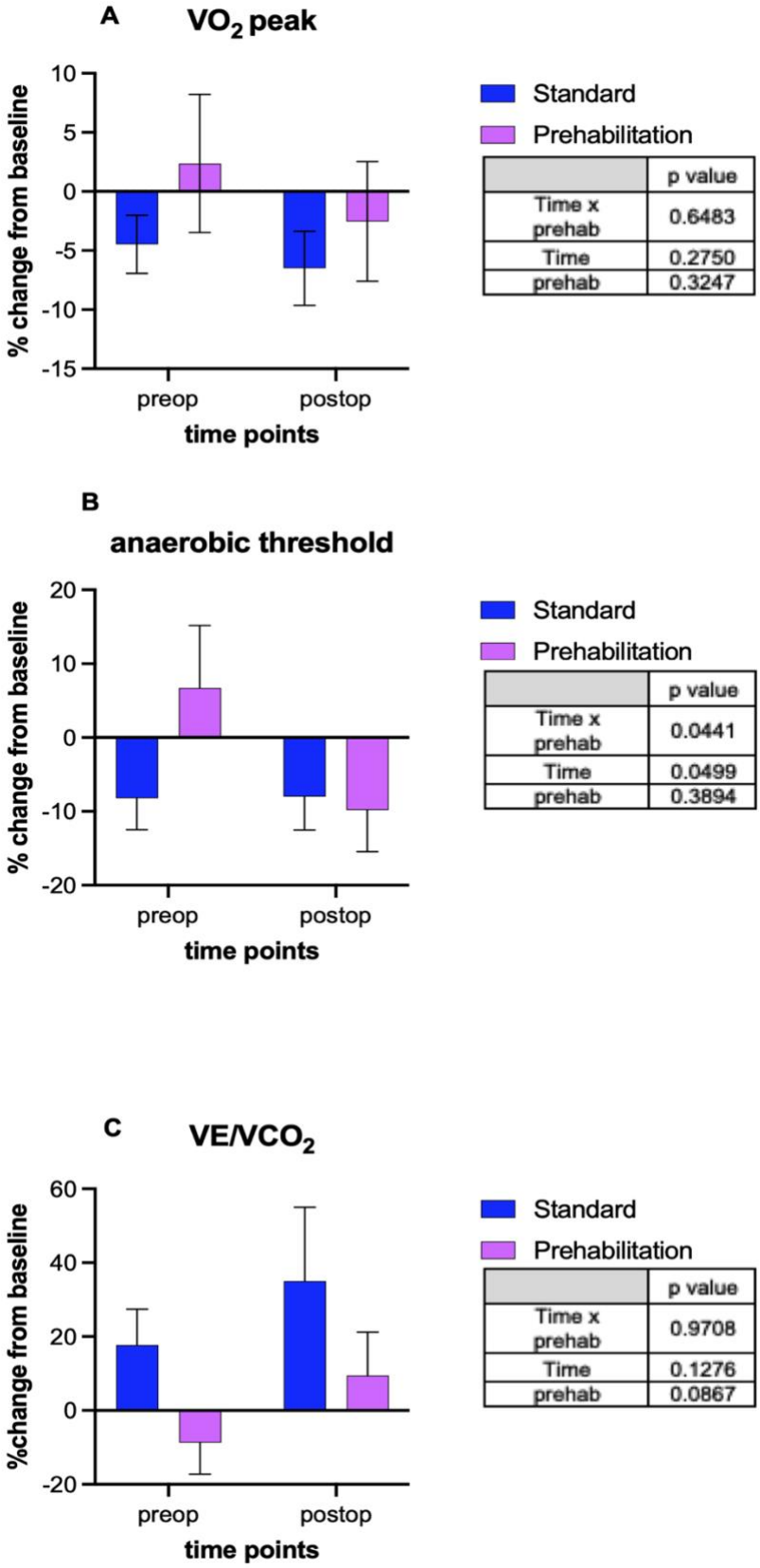


Figure 4-6 Multi-comparison ANOVA analysis of CPET variables

4.3.5 Comparison of body composition in the standard vs. prehabilitation group

A subgroup (50%) of the entire study cohort had DXA body composition analysis (**figure 4-1**). The tables below summarise the percentage change from baseline in body composition between the groups.

Table 4.13 Mean % change in body composition from baseline to pre-op (standard vs. prehabilitation)

Variable	mean % change from baseline Standard vs. Prehabilitation Preop	95 % CI	P value
Total mass (kg)	11.30	-7.346 to 29.94	0.2266
Fat mass (g)	25.07	-8.559 to 58.71	0.1390
Lean mass(g)	5.500	-10.77 to 21.77	0.4968

CI: confidence interval, DXA: Dual energy x-ray absorptiometry, p value: probability value

Table 4.14 Mean % change in body composition from baseline to post-op (standard vs. prehabilitation)

Variable	mean % change from baseline Standard vs. Prehabilitation Post-op	95 % CI	P value
Total mass (kg)	13.33	-5.314 to 31.97	0.1554
Fat mass (g)	13.50	-20.13 to 47.13	0.4203
Lean mass(g)	11.21	-5.062 to 27.48	0.1706

CI: confidence interval, DXA: Dual energy x-ray absorptiometry, p value: probability value

Table 4.15 Comparison of % change in body composition from baseline between pre-op & post-op in the standard and prehabilitation group.

Variable	mean % change from baseline	P value		mean % change from baseline	P value
	Standard			Prehabilitation	
	Pre-op vs. Post-op (95% CI)			Pre-op vs. Post-op (95% CI)	
Total mass (kg)	-2.544 (-22.73 to 17.64)	0.7935		-0.5117 (-19.66 to 18.64)	0.9557
Fat mass (g)	10.47 (-26.55 to 47.50)	0.5585		-1.097 (-36.23 to 34.03)	0.9482
Lean mass(g)	-6.413 (-22.74 to 9.913)	0.4187		-0.7033 (-16.19 to 14.79)	0.9248

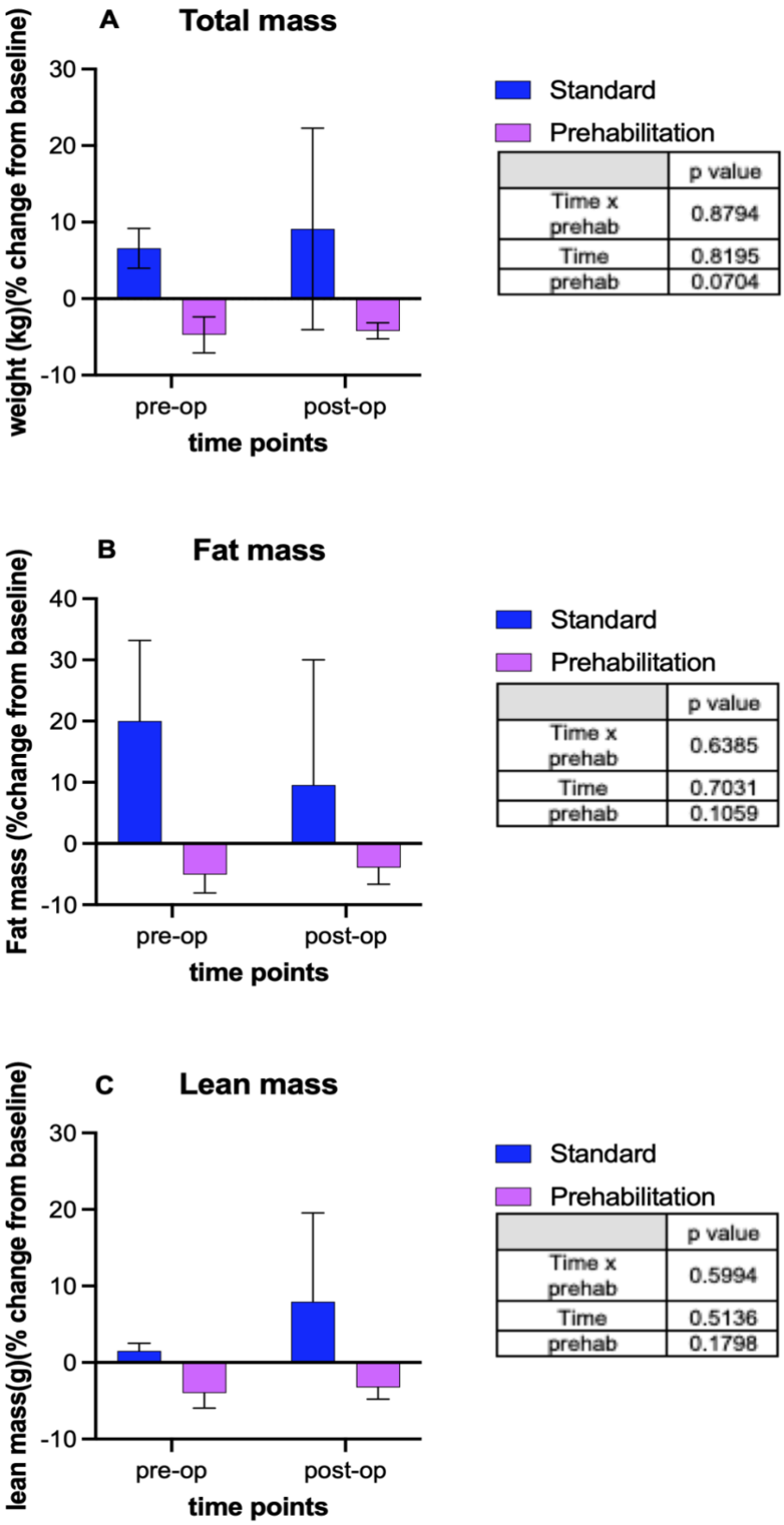


Figure 4-7 Multi-comparison ANOVA analysis of body composition variables

4.3.6 Comparison of hand grip strength in the standard vs prehabilitation group

The tables below summarise the differences in handgrip strength between the groups

Table 4.16 Mean % change in HGS from baseline to pre-op (standard vs. prehabilitation)

Variable	mean % change from baseline Standard vs. Prehabilitation **Preop**	95 % CI of difference	P value
Handgrip Strength (kg)	-4.306	-11.20 to 2.591	0.2171

CI: confidence interval, HGS: handgrip strength, p value: probability value

Table 4.17 Mean % change in HGS from baseline to post-op (standard vs. prehabilitation)

Variable	mean % change from baseline Standard vs. Prehabilitation **Post-op**	95 % CI of difference	P value
Handgrip Strength (kg)	-3.451	-9.999 to 3.097	0.2966

CI: confidence interval, HGS: handgrip strength, p value: probability value

Table 4.18 Comparison of % change in body composition from baseline between pre-op & post-op in the standard and prehabilitation group.

Variable	mean % change from baseline	P value		mean % change from baseline	P value
	Standard			**Prehabilitation**	
	Pre-op vs. Post-op (95% CI)			Pre-op vs. Post-op (95% CI)	
Handgrip strength (kg)	1.080 (-4.827 to 6.988)	0.7111		1.935 (-3.786 to 7.656)	0.4946

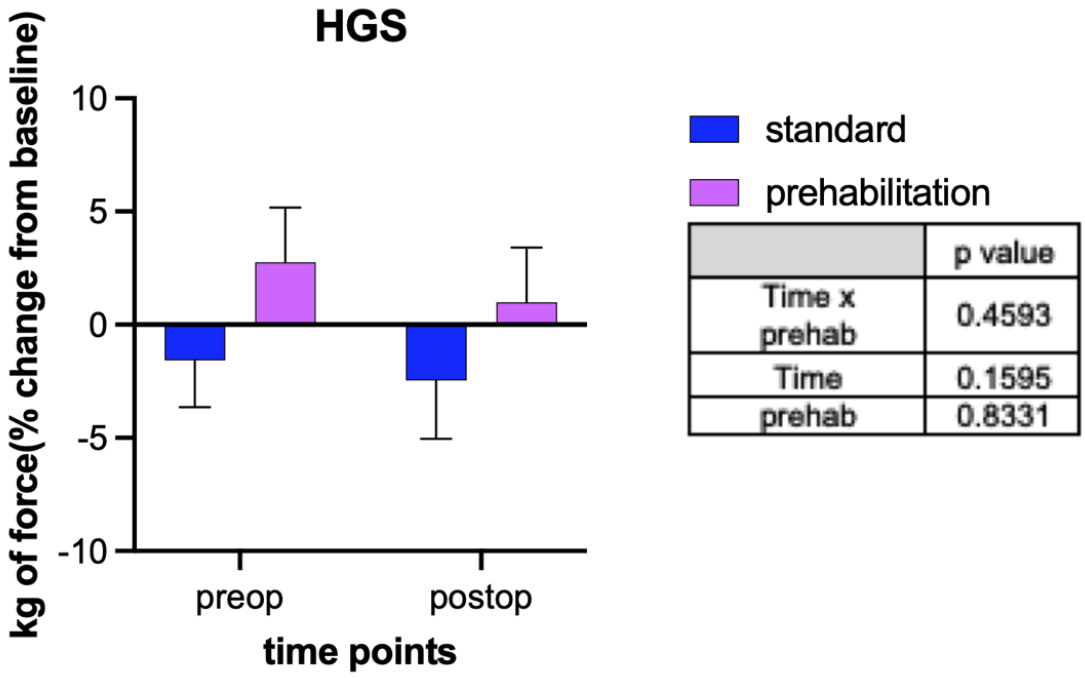


Figure 4-8 Multi-comparison ANOVA of HGS

4.3.7 Comparison of length of hospital & Intensive care stay between groups and cohorts

The figure below summaries the difference in length of hospital and intensive care stay between the groups(standard vs. prehab) and between the cohorts(CR vs HB).

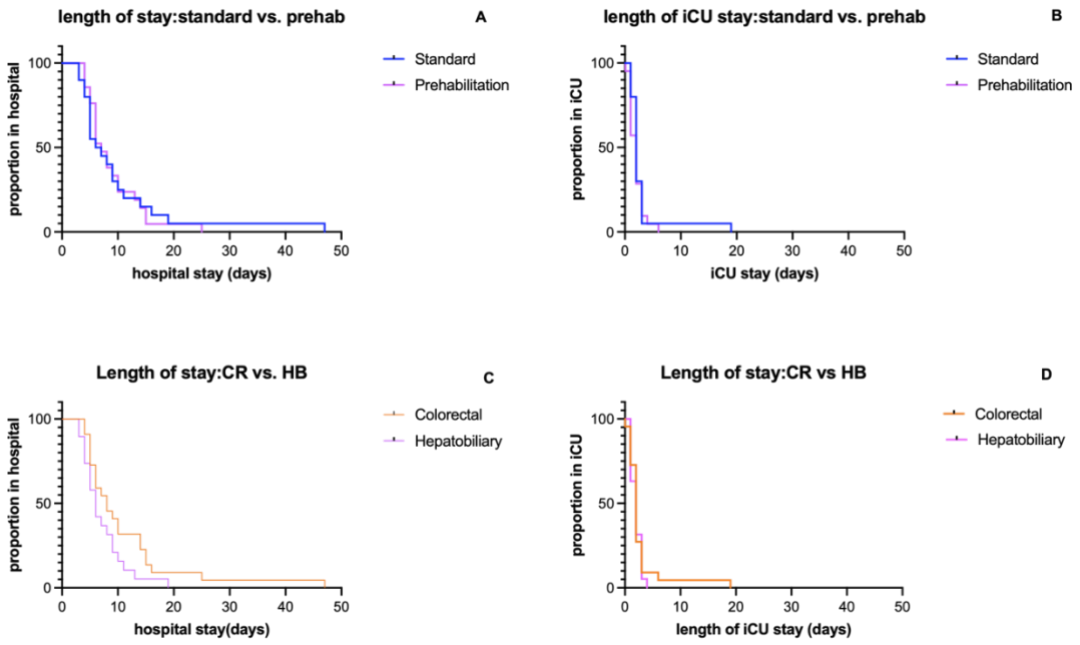


Figure 4-9 Length of hospital & ICU stay **A**: length of hospital stay; standard vs prehabilitation (95% CI 0.5347 to 1.819 p = 0.9616). **B:** length of iCU stay; standard vs. prehabilitation (95% CI 0.4468 to 1.525 p = 0.3905). **C**: length of hospital stay; CR vs. HB (95% CI 0.3162 to 1.149 p = 0.0710). **D**: length of iCU stay; CR vs. HB (95% CI 0.4817 to 1.656 p = 0.6073)

4.3.8 Comparison of CD III & IV complication rates between groups and cohorts

The figure below summarises the difference in complication rates between the groups. There was no statistically significant difference in complication rates between the groups.

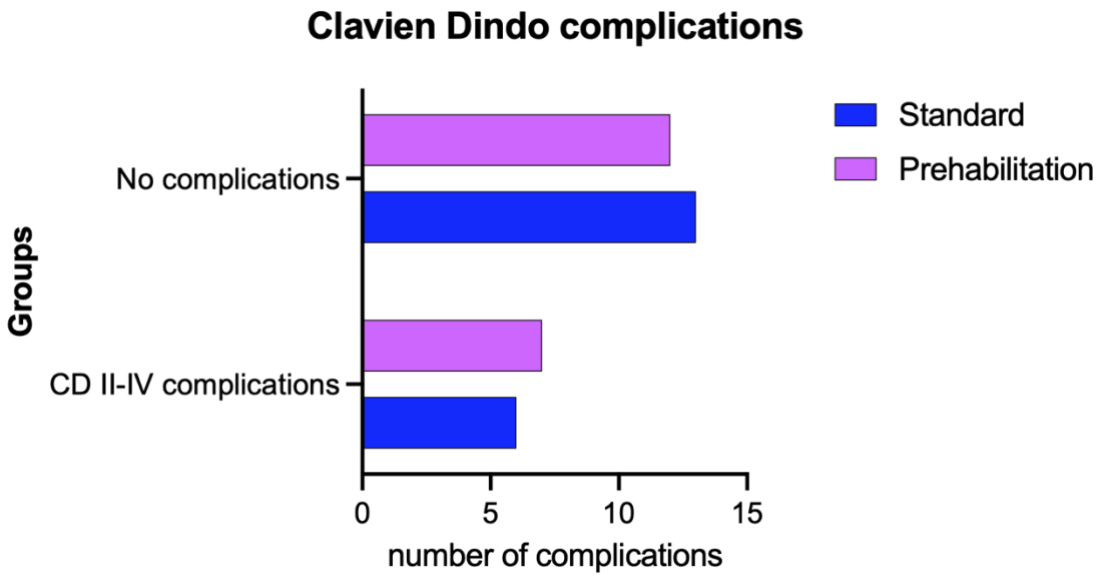


Figure 4-10 Comparison of clinically relevant Clavien-Dindo complications: standard vs. prehabilitation: (odds ratio 0.7912 95% CI 0.2339 to 3.356 p = >0.9999)

4.4 Discussion

There was an observed trend towards increased PAI-1 & leptin levels and decreased insulin concentrations from baseline to preoperatively in the standard group (**figure 4-4** A,D,H). Within the same time period, in the prehabilitation group, no significant differences were found for all cytokines/signalling proteins from baseline to preoperatively (**table 4.4**). A similar increasing trend was observed for C-peptide postoperatively in the standard group while this change remained flat in the prehabilitation group (**table 4.5**).

Within the patient recovery period (between preoperative & postoperative time points) there was a statistically significant increase in PAI-1 & leptin and a decrease in C-peptide in the standard group. In comparison to prehabilitation at the same time interval, the concentrations of these cytokines were not statistically significantly different. In the standard group there was an observed trend toward increased TNF-α levels in the same time period. In the prehabilitation group there was trend of increased active GLP-1 levels, with a

non-significant decrease in the standard group within that time period (**table 4.6**).

There were no statistically significant changes in blood biochemistry from baseline to preoperatively/postoperatively between the groups (**figure 4-5** A-J). There was a trend towards reduced folate levels in the standard group in the preoperative period when compared to prehabilitation (**table 4.7**).

Interestingly in the recovery period there were statistically significant decreases in urea, creatinine and albumin levels in both groups, likely reflecting the physiological changes related to surgery. In addition, within this time period there were statistically significantly lower copper levels and higher bilirubin concentrations in the standard group compared to prehabilitation. There was also a statistically significant decreased in haemoglobin and an increase in alkaline phosphatase in the prehabilitation group compared to standard (**table 4.9**)

When CPET variables were assessed there was a trend towards reduced AT in the standard group compared to prehabilitation preoperatively. There were no significant differences in the other CPET parameters (**table 4.11**). However postoperatively there was a statistically significant increase in AT in the prehabilitation group when compared to standard (**table 4.12**)

When assessed from baseline, there was a non-significant decrease in total mass, fat mass and lean mass preoperatively and postoperatively in the prehabilitation group when compared to standard. Interestingly in the case of total mass, fat and lean mass in the recovery period there was an increase in the standard group, whereas weight remained relatively unchanged in the prehabilitation group (**figure 4-7 A,B & C**).

Form baseline there was a modest deterioration in HGS in the standard group when compared to prehabilitation where there was also a modest increase (**figure 4-8**), however this was not statistically significant. In the recovery phase there was a further non-significant decrease in HGS in the standard group when compared preoperatively. Within the same time period this decrease was also

noted in the prehabilitation group. There was no difference in LoS (ICU or hospital) or clinically significant complications between the groups.

4.5 Conclusions

These data has demonstrated that prehabilitation appears to inhibit PAI-1 & leptin levels and prevents a decline in C-peptide concentrations. PAI-1 is known to promote clot formation through fibrinogenesis. This suggests that moderate intensity exercise training may be protective against thrombotic events especially in the recovery phase when these events are more likely. These data also suggest an exercise-mediated reduction of leptin concentrations possible via the loss of adipose mass. The reduction in the total mass, fat and lean mass in the prehabilitation group provides evidence of this interaction. C-peptide represents a valid measure of insulin secretion and promotes anabolic effects. The prevention of decline in C-peptide could suggest that prehabilitation may promote physical resilience by counteracting the catabolic effects of surgery.

The declines in urea, creatinine and albumin levels in the recovery phase might reflect the catabolic effects of surgery. Prehabilitation appears to protect against depletion of copper levels which suggests a potential immune-protective effect. This observation may require further investigation.

Concerning CPET variables this study has demonstrated a statistically significant increase in AT in the prehabilitation group in the recovery period. Although this finding was not associated with reduced LoS, complication rates or mortality, there may be medium or long-term benefits not realised within the scope of this trial.

Taking all the findings together, overall these data suggest that prehabilitation may be associated with improved cardiovascular fitness through its effect on AT and cytokine-mediated (PAI-1) vascular protective effects. This is the first study to describe these cytokine-mediated effects within a prehabilitation population and warrants further investigation.

Chapter 5: General Discussion

5.1 The case for prehabilitation

Preliminary qualitative and quantitative studies suggest that there are benefits (reduced length of stay, improved cardiorespiratory function, reduced postoperative complications and improved quality of life) when prehabilitation is used within the context of cancer care[7,22,69,201]. In 2017 Macmillian Cancer Support developed a strategic 'Evidence and Insight' review on prehabilitation[10]. The outcome of this was to incorporate prehabilitation into routine cancer care and to develop principles and guidance for prehabilitation. This study aims to support this vision and answer some of the questions on the patients who are most likely to benefit from prehabilitation and to quantify some of these benefits by investigating the molecular processes that influence clinical changes.

This study primarily sought to assess the biological and physiological impact of an exercise & nutrition prehabilitation intervention. As described in chapter 1, biological signalling pathways are thought to play a role in influencing some clinical outcomes such as wound infection[194] and may have a role to play in disease recurrence and survival. Aerobic fitness also has a key role to play in the ability to endure surgical stress and CPET variables are known to be associated with some survival outcomes as detailed in chapter 2. This study also assessed secondary outcomes including hospital stay (LoS), complications and quality of life (QoL). The psychosocial adaptation to prehabilitation was not addressed in this thesis and will form the basis of a separate manuscript.

There is conflicting evidence on the benefits of prehabilitation as a pre-operative intervention. Several studies reported on improvements in cardiopulmonary exercise test (CPET) variables after supervised pre-operative exercise programmes[7,69,78]. Some of the other measured variables such as functional capacity were sustained in the short to medium term[5,202]. Other studies reported reduced length of stay (LOS)[12,68] and reduced complication rates[19]. While no studies have suggested that prehabilitation has a deleterious effect on

outcomes a few studies have showed that there is no difference in outcomes between standard care and prehabilitation[3,19]. It is unclear from the literature as to what are the optimum levels of exercise and nutrition that may lead to clinically relevant improvements. This may be partly explained by the fact that the humoral and adaptive immune responses to nutrition and exercise are not fully understood. We may be able to better understand 'how' and 'why' some prehabilitation interventions work by linking measured molecular responses to observed clinical outcomes. This randomised controlled trial aimed to focus on understanding how biochemical and physiological adaptations brought about by exercise and nutrition may influence clinical outcomes in patients undergoing elective HB and colorectal cancer surgery.

5.2 The biological effect of prehabilitation

Revisiting the study hypothesis, the main findings from the SPECS trial were the suppression of PAI-1, and a reduction in leptin and protection of C-peptide levels. PAI-1 has been of interest due to its association with metabolic disorders such as diabetes, dyslipidaemia and hypertension[203]. It has also been studied within the context of peripheral arterial disease with reducing levels correlating with reduced incidence of cardiovascular morbidity[204]. Raised levels have been reported to increase the risk of cardiovascular events and higher values being prevalent in sedentary patient groups. One study has suggested that moderate intensity training can lower PAI-1 levels which may have a cardiovascular protective effect[205]. This reflects our findings and further, the SPECS exercise programme duration has illustrated that this can be achieved between 2-5 weeks of training. Of interest is the suggestion that shorter moderate intensity exercise volumes of 10 days have not been shown to reduce PAI-1 levels in other studies[206]. Although further work is required in this area to determine the minimum volume of exercise required, the SPECS data suggest that 2 weeks may be a putative minimum.

The role of C-peptide in glucose homeostasis and cell growth and signalling has been the subject of enquiry for some time. Work in animal models have suggested its potential role in insulin-mediated cell growth and anabolic

characteristics[207]. The fall in C-peptide levels seen in the recovery phase in standard was not apparent in the prehabilitation group. This suggests that prehabilitation may maintain C-peptide levels. While the mechanism of this interaction is unclear, a potential explanation could be that exercise training builds physiological resilience pre-operatively which may limit the catabolic effects of surgery and this is maintained in the weeks after surgery.

Leptin is known to be synthesised by adipose tissue and has a role in modulating metabolism and energy balance[208]. Unsurprisingly prehabilitation led to a reduction in fat mass which manifested with lower levels in the prehabilitation group. Although the SPECS trial was not powered to detect statistically significant reduction in fat mass, the decrease noted in prehabilitation is important as related to the metabolic effect of adipose previously discussed in chapter 1. Future prehabilitation studies with larger sample sizes may choose to examine this area further to determine how the metabolic activity of adipose tissue relates to carcinogenesis and clinical outcomes.

5.3 The physiological effect of prehabilitation

The SPECS trial has demonstrated that prehabilitation improved cardiovascular fitness as measured by AT. The magnitude of this improvement measured as the percentage increase from baseline measured postoperatively was 16.53 % (CI 5.15 to 27.90) p = 0.0056. This change represents 0.5-2.7 ml/kg/min improvement in AT. Similar improvements have been seen in other studies[7,186], however these data has demonstrated that this can be achieved with moderate intensity training over a 2 to 5-week period.

5.4 The impact of prehabilitation on body composition

Although groups were well matched for BMI (**table 4.4**), the mean weight in the prehabilitation group was 20% higher than standard (standard vs. prehabilitation) 76.06 vs. 90.62 95%CI 2.817 to 26.30 p = 0.0019. Prehabilitation was associated with a non-significant reduction in total mass, fat mass and lean mass. These pilot data suggests that DXA can be a useful tool

in assessing response to an exercise due to its ability to categorise what type of weight is lost and where it is lost from. A post hoc analysis determined that 64 patients would be required in each group to detect a statistically significant difference (effect size 0.5 and α 0.05, 1-β = 0.80) in body composition parameters.

5.5 The impact of prehabilitation on handgrip strength

HGS was assessed as a secondary outcome. There was no statistically significant difference in mean percentage change in HGS between the groups(**figure 4-8 chapter 4**). However the prehabilitation group recorded higher values in kilograms of force compared to the standard group at baseline (37.43 vs. 35.76, mean difference(MD) 1.669 ± 3.137 95% CI -4.676 - 8.013 p = 0.597), preop (37.72 vs. 34.53, MD 3.191 ± 3.558 95% CI -4.056 - 10.44 p = 0.376) and postop(36.95 vs. 35.82, MD 1.132 ± 2.953 95% CI -4.857 - 7.120 p = 0.703). This likely reflects the statistically significant higher body mass in the prehabilitation group as detailed in the previous section.

HGS may be viewed as a proxy for skeletal muscle quality and function. Studies have shown that reduced levels of HGS correlate with poorer outcomes after abdominal cancer surgery[209]. This correlation was not seen in the SPECS trial and one explanation for this could be that the study was not powered to detect this change.

5.6 Perioperative Outcomes

Complication rates, LoS in intensive care & hospital and 90-day mortality were assessed as secondary outcomes. There was no statistically significant difference in CD $\geq$ III complications between standard and prehabilitation.

Major liver resections routinely involve periodic occlusion of the blood vessel supply to the liver by way of a Pringle manoeuvre which may facilitate safer parenchymal transection and reduced blood loss[210]. Combined with a low central venous pressure employed as an additional haemodynamic measure, HB patients may experience bouts of liver ischaemia and reduced venous return

that may have global physiological effects[211]. These effects are unique to liver surgery, presenting a technical and operative difference between HB and CR resections. Consequentially it was important to assess these groups separately for complications. On further assessment of type of operation (HB vs. CR) as a subgroup, there were a greater proportion of serious complications recorded in the HB group (4/19) 21% vs CR (1/21) 4.7%, however this was not statistically significant (odds ratio 0.270 95 % CI 0.020 - 2.214 p = 0.354). For the 4 patients in the HB group having serious complications, there was a return to theatre for small bowel obstruction, percutaneous drainage for bile leak, post- operative bleeding requiring cardiovascular support and long-term postoperative ileus requiring total parenteral nutrition (TPN). In the CR group there was 1 clinically significant case of respiratory failure requiring bronchoscopy. The HB group reported 2 hospital-acquired respiratory tract infections (CD I & II). In the CR group of the 9 CD I & II complications, 6 were for paralytic ileus, 3 for wound or organ space infections.

There was no statistically significant difference in LoS between the groups and no reported 90-day mortalities. These findings are in keeping with previous studies that have assessed the effect of prehabilitation in these study groups[6,7]

5.7 Study group variations

There were several variations within and across the groups that were taken into consideration. It was important to clarify peri-operative receipt of chemo or radiotherapy as published data suggests that in both the neoadjuvant and adjuvant settings these treatments may affect physical and metabolic function[212] and as such CPET values of the study groups. It is also unclear as to the impact of chemotherapy on body composition. Published data suggests that the gastrointestinal side-effects of some chemotherapy agents may reduce total body weight by their overall effect on appetite and gut function[213]. It is also well documented that patients undergoing these therapies may experience a wide spectrum of other side-effects such as muscle ache and weakness, neutropenia, and alterations in the gut microbiome that may explain post-operative complications such as paralytic ileus, surgical site and organ space

infections[214]. These findings raise the opportunity to further investigate whether the addition of food supplements that protect the gut microbiome could be part of intervention arms for future prehabilitation studies.

In the standard group (7/20) 35% of patients had neoadjuvant therapy versus (6/21) 28% in the prehabilitation group (odds ratio 1.346, 95%CI 0.334 - 4.464 p = 0.7442). For adjuvant therapy, in the standard group (8/20) 40% versus (8/21) 38% in the prehabilitation group (odds ratio 1.083, 95 %CI 0.308 - 3.829 p = >0.999). It was not possible to ascertain the extent to which neoadjuvant/adjuvant therapies may have had an influence on circulatory cytokines, CPET and body composition variables as this was beyond the scope of the study. However both groups were equally matched as far as receipt of neoadjuvant/adjuvant therapies hence diminishing the effect of bias.

The surgical modality (minimally invasive (MI) or open) employed is known to affect some clinical parameters such as operative time, wound infection, post-operative pain and time to recovery. In the SPECS trial (12/20) 60% of patients in the standard group had a MI approach (laparoscopic or robotic), while (6/20) 30% had laparoscopic converted to open. For the prehabilitation group (16/21) 76% minimally invasive and (5/21) 23% laparoscopic converted to open. There were no open procedures recorded in the prehabilitation group. Overall there was no statistically significant difference in the MI modality; standard vs prehabilitation (odds ratio 0.468, 95% CI 0.124 - 1.836). However due the higher proportion of MI procedures in the prehabilitation group, the operative times were compared with standard. This revealed a mean operating time of 357 minutes standard vs. 473 prehabilitation (mean difference 115 +/-55.9) 95% CI 2.270 - 228.4 p = 0.045. This finding was similar to previously reported studies that reported increased operative times with MI procedures. Within the SPECS trial this increased operative time did not translate to longer recovery times or complication rates as reported in other studies[215,216].

With the advent of robotic approaches, the proportion of patients having MI procedures is likely to increase. As MI operating platforms gain wider uptake there is the expectation that major abdominal surgery operative times to

increase further when compared to other modalities. This increase may reflect the time associated with gaining competence and confidence as surgeons traverse across their respective learning curves[217]. This study has not sought to demonstrate whether increased anaesthetic times may have an impact on functional recovery. However learning from data on perioperative medicine it would be reasonable to suggest that prolonged anaesthetic and surgical times may have a greater risk of deleterious effects on high risk patients and prehabilitation may have a role to play in mitigating some of these effects[218].

5.8 Recruitment Rates

The trial recruited sufficient numbers to power the primary outcome measures. Over a 2-year study period, 43 patients were recruited despite several barriers to recruitment detailed in section 4.2.6.Of particular note were exclusions for patients who did not possess or have access to a mobile phone, tablet or computer. Although the research team made provisions for providing tablets for this purpose, time constraints, difficult logistics of training participants to use this and communication only via post made that group difficult to recruit. This aspect of recruitment requires further evaluation and strategies to broaden access to such trials by earlier recognition of technology-related, educational and socioeconomic factors that may pose barriers to participation. Ultimately under-representation of such groups may lead to limited generalisability of findings.

5.9 Exercise & Nutrition Compliance

The physiological changes that underpin the physical benefits of exercise are likely to involve utilisation of substrate(carbohydrates, fats, proteins and micronutrients) to build muscle and aerobic endurance. It was important to establish baseline levels of activity and nutritional intake as the evidence suggest that these work in a complementary way[219]. An exercise compliance rate of 98% was recorded based on review of participant exercise logs and corroborating this with accelerometry data. This compliance rate was considerably higher than figures quoted in other prehabilitation trials[220]. A

reason for this may have been the combination of type of exercise (moderate intensity) and a personalised approach to exercise employed by the study personal trainer. This patient-centred approach has been cited as a strategy to improve exercise adherence[221]. Through this approach it is likely that patients felt empowered and were highly motivated to complete the intervention.

A major challenge in delivering the SPECS trial was ensuring a uniform volume of moderate intensity exercise. There was wide variation in the number of days available for prehabilitation. While the protocol stipulated a minimum of 2 weeks availability for exercise intervention, 3/21 (14%) patients had < 2 weeks due to their operation dates being brought forward by the parent cancer care teams after being enrolled on the study. This practice reflects practical and logistical considerations that are commonplace throughout surgical units in the NHS and possibly highlights the importance of commencement of prehabilitation strategies much earlier in the cancer care pathway. It also brings into focus as to how prehabilitation may be integrated into 'fast track' cancer care pathways which inevitably further reduce the time available for pre-operative optimisation. The majority of patients 18/21 (86%) had 2-5 weeks of prehabilitation. It is the authors view that due to differences in cancer types, pre-operative workups, requirement for neoadjuvant therapy and patient factors it would be very challenging to achieve a uniform volume of exercise in mixed cancer cohort as in the SPECS trial. To ameliorate this potential issue several other studies have addressed a single cancer group such as locally advanced rectal cancer as in the Empower trial[186] or CRLM[7]. However the practical nature of the SPECS trial allowed for deeper examination of the 'real world' challenges and how a prehabilitation programme performs across a cross-section of surgical patients. This approach aligns with the Evidence & Insight Strategy mentioned previously in **section 5.0**.

At the start of the trial patients were guided and given download and use instructions for a calorie counter app which substituted a written food diary. Compliance with this as a way to monitor macro/micro nutrients was poor and had to be abandoned early after commencement. Previous nutrition-based trials have suffered from a similar lack of adherence data[222] and represents a

potential challenge for future studies. The trial dietician was instrumental in guiding the nutrition aspect in the prehabilitation group. The main aspect of the nutrition intervention involved bespoke advice with the main objective of promoting better quality calorie intake and ensure micronutrient balance. All patients within the prehabilitation group received counselling from the trial dietician.

5.10 Study limitations

There were several factors encountered that may have contributed to bias. The nature of the intervention may have inadvertently attracted a subset of patients who were fitter, more motivated and more likely to complete the exercise component. This phenomenon was not particularly unique to this study and has been extensively reported on in the literature[223].

Another unavoidable recruitment bias was the effect of the Covid-19 pandemic. Restrictions due to the virus had a dual impact on recruitment. First, local operative guidelines suggested that frail patients who were most at risk of peri-operative complications be managed with alternative treatments such as chemotherapy and other non-operative interventions. This was a group of patients who would have otherwise been eligible for the Trial. Consequently, high-risk groups are more likely to benefit from optimisation interventions such as prehabilitation, and the lack of statistical differences seen in primary outcomes may reflect the relative absence of high-risk groups. Second was the logistical considerations of patients having to attend the hospital site for assessment visits and the risk that posed to contracting Covid-19 with the consequence of either their surgery being delayed or cancelled altogether. Even with risk reduction measures the study PI had to balance ethical and legal considerations of patients participating in the Trial while maintaining national restrictions such a quarantine prior to surgery. The author has tried to capture the potential number of patients who may have been excluded exclusively this to this effect (see Consort in Chapter 3).

A small proportion of patients although motivated to participate in the study, did not possess a mobile phone, tablet, computer or internet connection to allow for remote delivery of the exercise programme. Although the research team had made allowances to provide devices, the time limits of the study and logistic barriers involved in being only able to communicate by post made this impossible to accomplish. Although the study PI did not detail as to whether this was a personal choice (not to acquire mobile technology), this potentially represents a barrier to participation in research and engagement with healthcare services in general.

A significant factor that affected the ability of the research team to complete CPET was the risk associated with carrying out the test as Covid-19 guidelines suggested that it was an aerosol-generating test and as such special adjustments had to be made such as fitting of a viral particulate filter. This led to considerable delays in performing CPET and inevitably missing data sets. The author has mitigated for this by carrying out Monte Carlo simulations to fill in missing data based on the premise that these data were missing due to the aforementioned reasons rather than patient-related reasons that could have influenced that actual outcome of the test.

Exercise activity in both groups was monitored using GeneActiv accelerometers. A combination of technical malfunctions and variations in patient wearing use meant that approximately 25% of the accelerometry data was partially recorded or missing. This amounted to 5 patients from each group. All participants were given detailed wearing instructions at baseline. Once the watches were retrieved on the day of the operation these aberrations could not be further mitigated. All participants also concurrently completed exercise logs which were collected and analysed after the prehabilitation period. To date this has been the largest study to use this technology within a prehabilitation setting.

5.11 Recommendations for future prehabilitation studies

Previous studies have demonstrated that exercise has no deleterious effects when used as the central part of prehabilitation. The SPECS trial has suggested

that moderate intensity exercise may lead to maintenance of lean mass in the peri-operative period which could have medium and longer team effects in patients being able to complete cancer treatments. With this in mind, future studies should assess difference types and volumes of exercise. Such studies may be able to clarify the minimum volumes and intensity of exercise required to induce biological adaptation and establish physiological changes. While HiiT training has demonstrated improved aerobic fitness in some cancer prehabilitation populations[7], this effect was not replicated in the colorectal cancer setting[224]. It is likely HiiT efficacy is based on adherence and may be suited for highly motivated patient groups. However there exists the exercise 'non-responder' effect which suggests that in some cancer groups even HiiT training may not lead to biological adaptation and improved fitness. Future studies would be well placed in investigating the genetic basis for this observation.

An important aspect of the impact of prehabilitation and its potential influence on medium and long-term survival may involve physiological resilience to chemotherapy. The relationship between total muscle (lean) mass and chemotherapy toxicity including patients' ability to complete chemotherapy cycles is an area of interest[212]. The literature in this area points to reduced tolerance to chemotherapy in patients with low lean mass and generally poorer outcomes in sarcopaenic patients[225]. The pharmacodynamics and kinetics of various chemo/radiotherapy regimes within the context of prehabilitation was beyond the scope of the SPECS trial and future work in this area would be useful. Nonetheless this study provides pilot data demonstrating how body composition may change after major surgery, and this may help guide the commencement of adjuvant therapy. This could be an important consideration if better timing for starting completion therapy could increase the yield of patients being able to complete these cycles.

The integration of wearable technologies as monitoring tools will be an important adjunct in measuring exercise dosing. These devices may also empower patients to better manage their activity and improve engagement with healthcare providers. If well integrated this may also allow for delivery of

bespoke interventions such as alterations in exercise programmes, interaction with other users, general information, guidance and coaching. The SPECS trial has suggested that a semi-supervised model with accelerometry monitoring is acceptable and scalable. These data has demonstrated that exercise programmes can be delivered remotely with high levels of adherence and there exists the opportunity to build on such a model.

5.12 Conclusions

Further work on understanding the mechanisms involved in cytokine and signalling protein interactions are needed. From the SPECS data there appears to be a response to PAI-1, leptin and C-peptide. The study has met its primary objective of detecting a MCID in AT. Larger prehabilitation studies are required to clarify the optimal exercise regime and minimal volumes of exercise required. Further it is clear that although programmes utilised within trail conditions have to be standardised, prehabilitation programmes in the future may have to be bespoke. Factors such as baseline fitness, accessibility to services, feasibility of exercise based on type of cancer, concurrent disease processes, time & availability of monitoring technology must be taken into consideration. Finally, several trials have now demonstrated non-inferiority of prehabilitation to standard. New technology may allow programmes to be delivered at scale with lower costs. There may be an argument to view prehabilitation as part of the ‘treatment’ paradigm for cancer, and in some cases, patients may even benefit from delaying surgery for an increased period of prehabilitation to offer the best possible opportunity to achieve improved outcomes

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Appendices

Appendix 1.0 The SPECS Trial Website

www.surgicalbridges.co.uk/SPECS

Appendix 1.1 Ethical Approval for the SPECS trial

NHS
Health Research Authority

Yorkshire & The Humber - Leeds East Research Ethics Committee
NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Telephone: 02071048103

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

26 April 2021

Mr Joel Lambert
Haslingden Road
Royal Blackburn Hospital
BB2 3HH

Dear Mr Lambert,

Study title:	**A mechanistic trial comparing Standard care versus Prehabilitation in patients undergoing Elective hepatopancreatobiliary (HPB) and colorectal Cancer Surgery: A feasibility study**
REC reference:	**21/YH/0069**
IRAS project ID:	**290723**

Thank you responding to the Research Ethics Committee's (REC) request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Appendix 1.2a/b Prehab Exercise Programmes

PREHAB ROUTINE A

Programme Frequency	3x per week	2x Pre-recorded / 1x Supervised via Zoom
Session Intensity	mod (60-75% HRmax)	Ideal aim for intensity and will be monitored throughout the session.
Session Duration	30-40mins	Warm up 5min / Main session 20min aerobic 10min resistance / 5 min cool down
Exercise Type	Aerobic and Resistance	Both Aerobic and Reistance will include bodyweight and light banded exercises
Equipment	Theraband Dumbbells Cans Chair	The participant can decide upon the equipment used depending on experience , condfidence, and enjoyment.

PREHAB ROUTINE A

WARM UP - 5 mins				
	EXERCISE	**TIME**	**EXERCISE NOTES**	**EQUIPMENT**
1	High Knees with arm movement	30-40s	March in place, moving arms in multiple directions warming up the shoulders and core. This exercise will increase heart rate and begin to moblise the ankles, knees, hips, lower back, and shoulders.	BW
2	Side to Side Shuffle with Knee Raise	30-40s	Whilst standing, move sideways for a few steps, raise the inside leg, then replace and move the other direction repeating the same movement on the other side. This exercise will increase heart rate and introduce a single leg stance for balance.	BW
3	High Hurdles	30-40s	Whilst using a chair/table for support, raise the knee to the front and around opening the hips, return to standing position. This exercise will mobilise the hip joint and engage the abs.	BW/Chair
4	Up and Overs	30-40s	Hold the Theraband with straight arms infront of the hips, with out stretched arms, raise the arms up above the head and as far back as you feel comfortable, engage the abs the entire movement, return to starting position. This exercise will moblise the shoulder gurdle whilst engaging the core supporting posture.	Theraband
5	Sit to stand with tip toe reach	30-40s	Sit on the edge of a chair, stand up fully reaching to the ceiling with one or two arms, if need be hold onto anther chair or table to support balance. This exercise will focus on leg strength and balance.	BW/Chair
6	Shoulder Tap	30-40s	Leaning with both arms out stretched on a sturdy table, counter, or the stairs begin to tap oposite shoulders whilst keeping the hips flat to the ground. This exercise will focus on the core (abs, and lower back muscles)	Table

BW = Bodyweight DB = Dumbbells

PREHAB ROUTINE B

Programme Frequency	3x per week	2x Pre-recorded / 1x Supervised via Zoom
Session Intensity	mod (60-75% HRmax)	Ideal aim for intensity and will be monitored throughout the session.
Session Duration	30-40mins	Warm up 5min / Main session 20min aerobic 10min resistance / 5 min cool down
Exercise Type	Aerobic and Resistance	Both Aerobic and Reistance will include bodyweight and light banded exercises
Equipment	Theraband Dumbbells Cans Chair	The participant can decide upon the equipment used depending on experience , condfidence, and enjoyment.

PREHAB ROUTINE B

WARM UP - 5 MINS				
	EXERCISE	**TIME**	**EXERCISE NOTES**	**EQUIPMENT**
1	High Knees with arm movement	**30-40s**	March in place, moving arms in multiple directions warming up the shoulders and core. This exercise will increase heart rate and begin to moblise the ankles, knees, hips, lower back, and shoulders.	BW
2	Side to Side Shuffle with Knee Raise	**30-40s**	Whilst standing, move sideways for a few steps, raise the inside leg, then replace and move the other direction repeating the same movement on the other side. This exercise will increase heart rate and introduce a single leg stance for balance.	BW
3	High Hurdles	**30-40s**	Whilst using a chair/table for support, raise the knee to the front and around opening the hips, return to standing position. This exercise will mobilise the hip joint and engage the abs.	Theraband/Cans /DB
4	Up and Overs	**30-40s**	Hold the Theraband with straight arms infront of the hips, with out stretched arms, raise the arms up above the head and as far back as you feel comfortable, engage the abs the entire movement, return to starting position. This exercise will moblise the shoulder gurdle whilst engaging the core supporting posture.	BW/Cans/DB
5	Sit to stand with tip toe reach	**30-40s**	Sit on the edge of a chair, stand up fully reaching to the ceiling with one or two arms, if need be hold onto anther chair or table to support balance. This exercise will focus on leg strength and balance.	Cans/DB
6	Shoulder Tap	**30-40s**	Leaning with both arms out stretched on a sturdy table, counter, or the stairs begin to tap the opposite shoulder whilst keeping the hips flat to the ground. This exercise will focus on the core (abs, and lower back muscles)	Table

Appendix 1.3 Ethical Approval from HRA

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Mr Joel Lambert
Haslingden Road
Royal Blackburn Hospital
BB2 3HHN/A

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

26 April 2021

Dear Mr Lambert

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**A mechanistic trial comparing Standard care versus Prehabilitation in patients undergoing Elective hepatopancreatobiliary (HPB) and colorectal Cancer Surgery: A feasibility study**
IRAS project ID:	**290723**
REC reference:	**21/YH/0069**
Sponsor	**East Lancashire Hospitals NHS Trust**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Appendix 1.4 Participant Information Sheet

Participant Information Sheet

Study Title: A randomised controlled trial comparing Standard care versus Prehabilitation in patients undergoing Elective hepatopancreatobiliary (HPB) and colorectal Cancer Surgery: A feasibility study

Short title: SPECS

Name of Researchers: Mr. Joel Lambert (Clinical Research Fellow)

Mr. Daren Subar (Consultant Surgeon)

Dr. Christopher Gaffney (Exercise & Sports Scientist)

Dr. Thomas Keegan (Director PG Research/Epidemiologist)

Dr. Rebecca Killick (Senior Lecturer in Statistics)

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?

Previous research suggests that exercise and nutrition may have beneficial effects for patients undergoing major cancer surgery. The purpose of our study is to better understand how these measures affect patients and to measure some of these potential benefits.

Why have I been invited?

You have been identified by your cancer care team as requiring surgery for a diagnosed cancer.

Do I have to take part?

It is up to you to decide whether to take part. Taking part in this research is entirely voluntary. If you do decide to take part you will be given this information sheet to keep

and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights.

When do I have to decide?

Within a week of seeing your cancer care team, you will receive a phone call from a member of the research team. If you agree to be part of the study, verbal consent will be taken over the phone. This will be followed up by formal written consent when you are first seen by a member of the research team.

What will happen to me if I take part?

You will be chosen at random to be in one of two groups (standard care or nutrition therapy and exercise). The table below shows the appointments you will be asked to attend. This will be the same in both groups.

Table 1. Appointments

Appointment Number	Reasons for Appointment
1	Baseline assessment: Blood test, CPET, BIA/DXA +/- muscle biopsy, QoL questionnaires
2	Just before your surgery: Blood tests, CPET, BIA/DXA +/- muscle biopsy
3	After your surgery: CPET, BIA/DXA +/- muscle biopsy, QoL questionnaires:

What is cardiopulmonary exercise testing (CPET)

Cardiopulmonary Exercise Testing (CPET) is a method used to assess the performance of the heart and lungs at rest and during exercise. During the CPET test you will be required to perform exercise on an upright bicycle whilst breathing through a mouthpiece. Each breath will be measured to assess how your body is performing. The capacity and strength of the lungs is measured before and during exercise. The heart tracing (ECG) will also be recorded prior to, during and after exercise.

The CPET test will last for a total of 40 minutes; however, you will only be required to exercise for approximately 10 minutes. The test requires your maximum effort to ensure the most reliable information is obtained. You will have this test on three occasions (at baseline, after your intervention and after surgery) if you are part of the

exercise and nutrition group. If you are part of the standard group your second CPET will be just before your surgery. You may have to travel to Lancaster University Human Performance lab for one or more of your CPET assessments. You will be reimbursed for travel costs and given guidance as to how to get there.

What is Bioelectrical Impedance Analysis (BIA)

This is a machine that measures the amount of fat and muscle in the body. You will be asked to stand on the machine and hold the side bars. After 20 seconds we will get a reading for body fat content. This measurement does not involve radiation.

Bioelectrical Impedance Analyser (BIA)

What is Dual Energy X-ray Absorptiometry (DXA)

This is a machine that measures the amount of fat and muscle in the body. It is more accurate than BIA. You will be asked to lie flat for 5 minutes and the machine will scan your body to give us detailed analysis of fat around your organs. If you take part in this study, you will have 2 to 3 DXA scans.

Some/all of these scans will be extra to those that you would have if you did not take part. These procedures use radiation to form images of your body and provide your doctor with other clinical information. This type of radiation can cause cell damage that

may, after many years or decades, turn cancerous. We are all at risk of developing cancer during our lifetime. The normal risk is that this will happen to about 50% of people at some point in their life. Taking part in this study will add only a very small chance of this happening to you.

Dual Energy X-ray Absorptiometry (DXA)

What is a biopsy

This is a small amount of tissue taken from the body. If you are eligible for the study you will be asked if you would consent to having muscle biopsies. This is optional. If you consent to having muscle biopsies, you will have some local anaesthetic applied to your thigh muscle to numb the area and a needle will be used to take a piece of muscle. The amount of muscle will be less than half the size of a pea. This will be analysed and allow us to assess your body's response to the interventions and also the impact of surgery on your body. You will have a biopsy before you start the study, during your surgery while you are asleep and after your surgery. We will take the smallest volume of tissue required to perform the analysis.

Blood tests

At your routine hospital appointments, blood tests will be taken to help us assess your nutritional state and other measures such as your blood counts.

Quality of Life (QoL) Questionnaires

Two questionnaires will be used to gain information on the psychological impact of illness and prehabilitation during the course of your treatment. This will take 10-15 minutes each to complete. You will be asked to compete these on 2 occassions: (on the day of your first appointment and within 6-8 weeks after your surgery (**table 1**. On page 2). You will have the option of completing this on the day or completing at home and posting back in a pre-paid envelope. You are under no obligation to complete this if questions cause you distress. If you do experience distress and require support please get in touch with the chief investigator, details given at the end of this document.

What groups may you be assigned to?

1. **Standard care +/- biopsy**

This will involve advice from your specialist nurse and automatic enrolment on the enhanced recovery programme. Your surgery will be explained in detail and you will be told what to expect before, during and after surgery. You will also have:

- Body composition measured by bioelectrical impedance analysis/DXA
- Asked to complete a food diary using a smartphone app
- Cardiopulmonary Exercise Test (CPET): a test of how well your lungs and heart work (three occasions)
- Muscle biopsy from the thigh (on three occasions)
- Quality of life questionnaires-QoL (two occasions)
- Follow-up assessment (6-24 weeks after surgery)

2. **Nutrition and Exercise Therapy +/- biopsy**

- Body composition measured by bioelectrical impedance analysis/DXA
- Interview by a dietician and anthropometric measurements taken and given dietary advice and information and Multivitamin (Forceval) for 8 weeks.
- Asked to complete a food diary using a smartphone app

- Cardiopulmonary Exercise Test (CPET): a test of how well your lungs and heart work (three occasions) at baseline, after the intervention period and in the follow-up period.
- Enrolled on a supervised exercise programme by a physiotherapist for a minimum of 2 weeks maximum 4 weeks. This will involve 5 min warm up followed by 20 min of aerobic training followed by 5 min cool down. Finishing with 10 min strength/resistance training.
- Muscle biopsy from the thigh (on three occasions)
- Quality of life questionnaires (two occasions): before and after surgery
- Follow-up assessment (6-24 weeks after surgery)

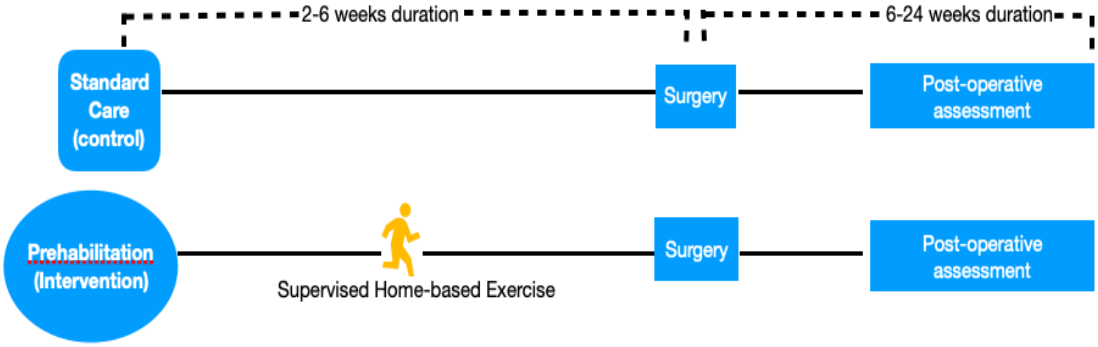
Surgery

You will have your surgery on the date given by your cancer care team as planned

Follow-up Assessment

On your routine follow-up appointment with your cancer care team, a research team member will speak to you about your experience of taking part in the study. You will be asked to complete quality of life questionnaires at the start and end of the study. This will either be given to you on the day to give written consent to the study or sent to you via post.

Trial Schedule



Screening Phone call

If you have considered taking part in the study and consent to be contacted, one of the research team will ask you some screening questions about your general health to

ensure you meet the criteria for inclusion into the study. If you are deemed ineligible for whatever reason this will be explained to you. If you are eligible you will be given a date to attend for formal consent and a baseline assessment. At that assessment you will be randomly assigned to the standard or exercise and nutrition group.

Food Diary

You will be asked to use a food diary app (NutraCheck) to record your dietary intake for a minimum of 3 days per week. This app is freely available and requires no personal identifiable information for its use. Only you will have access to your food diary. The only information you will be asked to input will be the amounts and types of food you eat for breakfast, lunch, dinner and snacks. At the end of the study you can print out this data or share it with us electronically.

Remotely Supervised Exercise Programme

This will involve an initial assessment by a physiotherapist or personal trainer to measure your baseline level of fitness and mobility and education on how to exercise safely at home. Using some information from your CPET test, an exercise plan will be given to you. This will be supervised by our physiotherapy team and a personal trainer remotely. The sessions will last for 40 minutes and will be done 3 times per week for a minimum of 2 weeks, maximum 4 weeks. You will be remotely supervised by a personal trainer for 1 day out of 3. The other two days you will have video recorded support from the same personal trainer. You will have a combination of aerobic exercises and strength training. Exercises will be designed based on your individual physical ability. You will need to have access to a smartphone, tablet, laptop or home computer with an internet connection. We recommend that during your exercise days that you are not on your own. For safety reasons we suggest a family member or friend being close by in the event of injury or need for medical attention.

Triaxial Acclerometry

This is a device that you wear on your wrist or ankle. It measures your movement throughout the day. It helps us measure your baseline level of activity. You will be asked to wear this device in both groups

Expenses

There is no payment for taking part in research but we will pay for parking and transportation charges arising out of hospital appointments for the research. We will ask you to keep a record of your receipts.

What are the possible disadvantages and risks of taking part?

Local anaesthetic will be injected under the skin before the biopsy needle is inserted. This may sting a little, but almost immediately will make the area numb. You may feel a movement under the skin when the needle is inserted, but you should not experience any discomfort. All procedures are carried out by experienced personnel routinely within our research group.

If you do suffer any other symptoms or you become in any way concerned prior to your next study visit or after the study has finished, you should contact the chief investigator, or any investigators named on this sheet prior to your next visit.

What are the possible benefits of taking part?

We cannot promise the study will help you but the information we get from this study may help provide evidence to support healthy lifestyles especially for patients undergoing cancer treatment. The study may also help us understand which interventions are most likely to benefit patients before surgery.

What happens when the research study stops?

Whichever arm of the study you participate in, you will be followed up as routine by your cancer care team as per national cancer follow-up guidelines.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by contacting the Patients Advisory Liaison Service (PALS).

How will we use information about you ?

We will need to use information from you and your medical records held by the hospital. We may also ask your GP for information for this research project.

This information will include your:

- First name and surname
- Your date of birth
- Your NHS number
- Your address
- Your phone number
- Other contact details such as: email address.

People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

Some of your information may be sent to other researchers in the field at the University of Nottingham, UK and the University of Lausanne, Switzerland. With your consent, anonymised scan data will also be shared with our collaborator General Electric (GE) for research and development purposes. They must follow our rules about keeping your information safe. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- If you choose to stop taking part in the study, we would like to continue collecting information about your health from central NHS records, your hospital and your GP. If you do not want this to happen, tell us and we will stop.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team listed below
- by sending an email to ig-issues@elht.nhs.uk, or
- by ringing us on 01254734488.

What will happen if I don't want to carry on with the study?

Your participation is voluntary and you are free to withdraw at any time, without necessarily giving any reason, and without your legal rights being affected. If you have consented to be part of the study but no longer want to participate in the assessments let us know. You can still be part of the wider study. If you want to withdraw entirely from the study, no further data will be collected but data already collected may be used for this study but no future studies.

What will happen to any samples I give?

Your biopsies and blood samples will be stored onsite at the ELHT pathology labs before transfer to Lancaster University labs for analysis. These samples will be stored anonymised. Samples will be stored for a period of 18 months. We will analyse all of your samples within our laboratories at Lancaster University. All analyses will take place during the period whilst we have ethical approval to conduct the research. Any samples remaining after ethics has ended will be disposed of in accordance with the Human Tissue Authorities codes of practice.

We will be working collaboratively with another researcher; Dr Rebecca Killick who is currently looking at better ways of analysing the fitness data that you will be providing. The numerical data of approximately 40 patients will be shared. This data will have no patient identifiable details.

Will any genetic tests be done?

No

What will happen to the results of the research study?

The results of this study will be incorporated into a Medical Doctoral thesis for a University research degree and will be published in relevant academic journals. Please be assured you will not be personally identified in any report or publication. You will

be invited to a non-formal 'results' evening at ELHT where refreshments will be provided. There we will explain our results in laymans terms. You will also be free to join in remotely via Zoom or Microsoft Teams. A summary of our findings will also be published on our study website www.surgicalbridges.co.uk/SPECS.

Who is organising and funding the research?

This research is being organised by Lancaster University in conjunction with ELHT who is the sponsor. The research is being funded by ELHT and Lancaster University. The money is used to pay for experimental running costs and analytical costs.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, and the Health Research Authority to protect your interests.

Further information and contact details

If you have any questions regarding the procedures involved in the above study, please do not hesitate to ask one of the investigators who will be happy to discuss.

Chief investigator: Mr. Joel Lambert
Clinical Research Fellow
Lancaster Medical School
Lancaster University
Lancaster, LA1 4YG
Phone: 01254 263555
Email: j.lambert1@lancaster.ac.uk; joel.lambert@elht.nhs.uk

Co-investigators: Mr. Daren Subar
Consultant hepato-pancreatobiliary Surgeon
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Haslingden Road
Blackburn BB2 3HH
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Co-investigators: Dr. Christopher Gaffney
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Lancaster Medical School
Lancaster University
Lancaster, LA1 4YG
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Email: c.gaffney@lancaster.ac.uk

Co-investigators: Dr Thomas Keegan
Director of Post-graduate Research/Clinical Epidemiologist
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Lancaster University
Lancaster, LA1 4YG
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Co-investigators: Dr Rebecca Killick
Senior Lecturer in Statistics
Department of Mathematics & Statistics
Lancaster University
B Floor , Flyde College
Lancaster, LA1 4YF
Phone: 015124593780
Email:r.killick@lancaster.ac.uk

Patient Advice Liaison Service (PALS)

Royal Blackburn Hospital
Haslingden Road
Blackburn
Phone: 0800 5872586
Email: complaints@elht.nhs.uk

Appendix 1.5 SPECS Consent form

SPECS Consent form V2.0 30/11/2020
IRAS no: 290723
clinicaltrials.gov

East Lancashire Hospitals NHS Trust | NHS | Lancaster University

Centre Number: ELHT

Study Number: 001

Participant Identification Number for this trial: SPECS_ _ _

CONSENT FORM

Title of Project: A randomised controlled trial comparing **S**tandard care versus Prehabilitation in patients undergoing Elective hepatopancreatobiliary (HPB) and colorectal Cancer **S**urgery: A feasibility study

Name of Researcher: Mr Joel Lambert, ELHT/Lancaster University

	Please initial box
1. I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that if I initially give consent but subsequently lose capacity during the study no further information will be collected, but initial information given will be retained for analysis	☐
4. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Lancaster University, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
5. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers (**optional**)	☐
6. I agree to my General Practitioner being informed of my participation in the study.	☐
7. I agree for my anonymised CPET data to be shared with a third party (Research group) (**optional**)	☐
8. I consent to having muscle biopsies to as per the study schedule (**optional**)	☐
9. I consent to tissue samples to be transferred to affiliate lab in Switzerland for specialist analysis (**optional**)	☐
10. I agree to take part in the above study.	☐

Name of Participant	Date	Signature

Name of Person taking consent	Date	Signature

Appendix 1.6 Patient participation letter to General Practitioner

IRAS no: 290723
SPECS V2 30/11/2020
clinicaltrials.gov NCT04880772

East Lancashire Hospitals NHS Trust | NHS Lancaster University

Letter to GP

dd/mm/yyy

Title of Project: A randomised controlled trial comparing **S**tandard care versus **P**rehabilitation in patients undergoing **E**lective hepatopancreatobiliary (HPB) and colorectal **C**ancer **S**urgery: A feasibility study

Dear Dr ....

Your patient……. has consented to take part in the above study. This study is investigating the impact of nutrition and exercise on clinical outcomes after cancer surgery. If you are happy for us to do so, we will provide updates on the progress of the study and present our findings on completion of the study.

If you require any further details including what participation will entail for your patient, please feel free to contact us using the details below. We have attached a patient information sheet for your interest.

Sincere regards

Mr. Joel Lambert BSc. MBChB MRCS MSc. FHEA
Chief Investigator SPECS study
Department of General & HPB Surgery
Royal Blackburn Hospital
Haslingden Road
BB2 3HH
Joel.lambert@elht.nhs.uk
01254263555

Appendix 1.7 Participant exercise log

Exercise Adherence log V1. 30/11/2020 IRAS 290723
Study ID: SPECS _ _ _
Date:

	Week 1		**Week 2**	
Supervised session	Date:		Date:	
	Time:		Time:	
Unsupervised session	Date:	Date:	Date:	Date:
	Time:	Time:	Time:	Time:

Appendix 1.8 SPECS trial randomisation log

Patient ID	Randomiser	Treatment group	Date time randomised
SPECS001	joel.lambert@elht.nhs.uk	B	21/05/2021 09:18
SPECS002	joel.lambert@elht.nhs.uk	B	02/08/2021 15:20
SPECS003	joel.lambert@elht.nhs.uk	A	24/08/2021 09:40
SPECS004	joel.lambert@elht.nhs.uk	A	10/09/2021 14:49
SPECS006	joel.lambert@elht.nhs.uk	B	30/09/2021 08:41
SPECS005	joel.lambert@elht.nhs.uk	A	02/10/2021 09:27
SPECS007	joel.lambert@elht.nhs.uk	B	07/10/2021 13:34
SPECS008	joel.lambert@elht.nhs.uk	A	13/11/2021 10:31
SPECS009	joel.lambert@elht.nhs.uk	B	02/12/2021 15:28
SPECS010	joel.lambert@elht.nhs.uk	B	14/01/2022 09:08
SPECS011	joel.lambert@elht.nhs.uk	A	15/01/2022 10:29
SPECS012	joel.lambert@elht.nhs.uk	B	15/01/2022 14:27
SPECS013	joel.lambert@elht.nhs.uk	A	21/01/2022 12:24
SPECS014	joel.lambert@elht.nhs.uk	B	21/01/2022 12:25
SPECS015	joel.lambert@elht.nhs.uk	A	28/01/2022 10:21
SPCES016	joel.lambert@elht.nhs.uk	A	16/03/2022 15:56
SPECS017	joel.lambert@elht.nhs.uk	B	17/03/2022 13:39
SPECS018	joel.lambert@elht.nhs.uk	A	23/03/2022 18:38
SPECS019	joel.lambert@elht.nhs.uk	B	24/03/2022 11:14
SPECS020	joel.lambert@elht.nhs.uk	A	24/03/2022 15:22
SPECS021	joel.lambert@elht.nhs.uk	A	19/04/2022 09:39
SPCES022	joel.lambert@elht.nhs.uk	A	19/04/2022 12:06
SPECS023	joel.lambert@elht.nhs.uk	B	19/05/2022 12:20
SPECS024	joel.lambert@elht.nhs.uk	B	26/05/2022 13:51
SPECS025	joel.lambert@elht.nhs.uk	B	16/06/2022 09:31
SPECS026	joel.lambert@elht.nhs.uk	A	16/06/2022 13:04
SPECS027	joel.lambert@elht.nhs.uk	B	14/07/2022 11:41
SPECS028	joel.lambert@elht.nhs.uk	A	25/07/2022 10:22
SPECS029	joel.lambert@elht.nhs.uk	B	03/08/2022 10:21
SPECS030	joel.lambert@elht.nhs.uk	B	05/01/2023 10:56
SPECS031	joel.lambert@elht.nhs.uk	A	12/01/2023 12:58
SPECS032	joel.lambert@elht.nhs.uk	A	27/01/2023 13:16
SPECS033	joel.lambert@elht.nhs.uk	B	09/02/2023 10:36
SPECS034	joel.lambert@elht.nhs.uk	A	10/02/2023 12:58
SPECS035	joel.lambert@elht.nhs.uk	B	30/03/2023 11:36
SPECS036	joel.lambert@elht.nhs.uk	B	30/03/2023 13:10
SPECS038	joel.lambert@elht.nhs.uk	A	17/04/2023 09:32
SPECS037	joel.lambert@elht.nhs.uk	A	18/04/2023 09:45
SPECS039	joel.lambert@elht.nhs.uk	A	07/06/2023 11:34
SPECS040	joel.lambert@elht.nhs.uk	B	04/07/2023 12:18
SPECS041	joel.lambert@elht.nhs.uk	A	04/07/2023 13:14:00
SEPCS042	joel.lambert@elht.nhs.uk	B	13/07/2023 09:01
SPECS043	joel.lambert@elht.nhs.uk	A	13/07/2023 10:21

Appendix 1.9 The SPECS Trial Website

www.surgicalbridges.co.uk/specs

Appendix 1.10 HRA Approval for retrospective CPET study

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Christopher Gaffney
Lecturer in Integrative Physiology
Lancaster University
Furness Building
LA1 4AT

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

01 March 2021

Dear Dr Gaffney

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Multivariate Time Series Classification of CPET for Improving Surgical Outcomes**
IRAS project ID:	**289915**
Protocol number:	**N/A**
REC reference:	**21/HRA/0600**
Sponsor	**Lancaster University**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.