

BMJ Open Prehabilitation in patients with cirrhosis awaiting liver transplantation: protocol of a feasibility study

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ABSTRACT

Introduction Patients with cirrhosis awaiting liver transplantation (LT) are often frail, and malnourished. The period of time on the waitlist provides an opportunity to improve their physical fitness. Prehabilitation appears to improve the physical fitness of patients before major surgery. Little is known about prehabilitation in patients with cirrhosis. The aim of this feasibility study will be to investigate the feasibility, safety, and effectiveness of a multimodal prehabilitation programme in this patient population.

Methods and analysis This is an open-label single-arm feasibility trial recruiting 25 consecutive adult patients with cirrhosis active on the LT waiting list of the McGill University Health Centre (MUHC). Individuals will be excluded based on criteria developed for the safe exercise training in patients with cirrhosis. Enrolled individuals will participate in a multimodal prehabilitation programme conducted at the PeriOperative Programme complex of the MUHC. It includes exercise training with a certified kinesiologist (aerobic and resistance training), nutritional optimisation with a registered dietician and psychological support with a nurse specialist. The exercise training programme is divided into an induction phase with three sessions per week for 4 weeks followed by a maintenance phase with one session every other week for 20 weeks. Aerobic training will be individualised based on result from cardiopulmonary exercise testing (CPET) and will include a high-intensity interval training on a cycle ergometer. Feasibility, adherence and acceptability of the intervention will be assessed. Adverse events will be reviewed before each visit. Changes in exercise capacity (6-minute walk test, CPET, liver frailty index), nutritional status and health-related quality of life will be assessed during the study. Post-transplantation outcomes will be recorded.

Ethics and dissemination The research ethics board of the MUHC has approved this study (2021-7646). Our findings will be submitted for presentation at national and international conferences, and for peer-reviewed publication.

Trial registration number NCT05237583.

INTRODUCTION

Frailty has emerged as a major predictor of worse outcome in patients with cirrhosis.¹ It is defined as a decreased physiological

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The feasibility, safety and effectiveness of a multimodal prehabilitation programme in patients with cirrhosis awaiting liver transplantation is unknown.
- ⇒ The PeriOperative Programme clinic of the McGill University has tremendous experience in leading prehabilitation clinical trials.
- ⇒ This carefully planned supervised multimodal prehabilitation will include exercise training, nutritional optimisation and psychological support.
- ⇒ Changes in objective measurements of exercise capacity, nutritional status and health-related quality of life will be assessed during the study.
- ⇒ This study which lacks a control arm will set the stage for a larger multicentre randomised controlled trial to specifically isolate the impact of prehabilitation in this patient population.

reserve and increased vulnerability to health stressors that predisposes one to adverse health outcomes.² It is associated with skeletal muscle mass depletion, progressive immobility, decreased energy expenditure and malnutrition. Current estimates indicate that sarcopenia and frailty are highly prevalent affecting 50% and 15%–40% of patients with cirrhosis awaiting liver transplantation (LT), respectively.^{3–5} The presence of frailty is independently associated with waitlist mortality, while worsening frailty also predicts increased pretransplant mortality.^{6–7} Pretransplant frailty is associated with worse post-transplant outcomes including death, hospital length of stay (LOS), intensive care unit LOS, non-home discharge and re-admission.⁸

Frailty is a well-known critical issue in the surgical literature where it was shown to be a predictor of complications and death.⁹ In a meta-analysis of nearly 700 000 patients, frailty quadruples the risk of postoperative mortality, and doubles the risk of major complications, re-operation, failed discharge and re-admission to hospital.¹⁰ A network meta-analysis



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of 5262 participants in randomised controlled trials concludes that physical intervention alone and physical intervention with nutritional supplementation are probably the most effective at reducing frailty, and improving health related quality of life (HRQoL) measures.¹¹ Unfortunately, the quality of evidence is low or very low, which advocates for further clinical trials.¹¹

Exercise is believed to have beneficial effects in patients with cirrhosis.¹² The role of multimodal prehabilitation combining exercise training, nutritional optimisation and psychological support, in patients with cirrhosis awaiting LT is unknown. This study will first assess if it is feasible and safe for patients on the liver transplant waiting list to participate in a multimodal prehabilitation programme. Second, it will determine if the prehabilitation programme can improve key preoperative markers of frailty. Finally, it will describe postoperative outcomes in those that underwent LT.

STUDY OBJECTIVES

Primary objective: feasibility

The primary objective of this study is to determine if it is feasible for patients with cirrhosis awaiting LT to participate in a multimodal prehabilitation programme combining exercise, nutritional optimisation and psychological support. To determine feasibility, we will: (1) assess the proportion of patients on the liver transplant list that would be eligible to participate in our study; (2) assess the proportion of eligible participants that are recruited into the study; (3) assess protocol adherence and loss to follow-up (LTFU) following study entry; (4) determine reasons for refusal to participate, lack of protocol adherence or LTFU.

Secondary objective: safety

The second aim of our study is to determine if it is safe for patients with cirrhosis awaiting LT to participate in a multimodal prehabilitation programme. For this, we will determine the incidence of serious and non-serious adverse events (AEs) during participation in the study, based on the Common Terminology Criteria for AEs version 5.0 classification.

Exploratory objectives: effectiveness of the intervention

The exploratory aims will evaluate if our multimodal prehabilitation programme has an impact on preoperative and postoperative outcomes. For this, we will assess if the intervention is associated with changes in preoperative markers of frailty, exercise capacity, muscle mass, nutritional status, HRQoL, and waitlist removal or death. We will also describe postoperative outcomes including complications, hospital LOS, discharge destination, re-admission and mortality at 3 months and 12 months in those that have undergone LT.

METHODS AND ANALYSIS

Study design

This is an open-label single-arm feasibility trial based at the McGill University Health Centre (MUHC),

Montreal, Canada. Consecutive adult patients followed at the Liver Transplant Clinic with cirrhosis active on the liver transplant list will be informed about the study by their usual treating hepatologist and will be approached for enrolment into a multimodal prehabilitation programme if they agree to be contacted by the study team. The prehabilitation programme will be conducted at the PeriOperative Programme (POP) complex. This study is approved by the MUHC Research Ethics Board (study ID 2021-7646).

Inclusion criteria

Patients with the following characteristics will be assessed for inclusion into the study: (1) age above 18 years; (2) diagnosis of cirrhosis, based on clinical, laboratory, imaging or histology findings; (3) active on the liver transplant waiting list of the MUHC; (4) signed informed consent form (ICF).

Exclusion criteria

Patients with any of the following characteristics will be excluded from participating into the study. Exclusion criteria are adapted from the safe exercise training guidance in patients with cirrhosis and include¹³: (1) Model for End-stage Liver Disease (MELD) >20; (2) acute hepatic decompensation within the last month (defined as variceal bleed, overt hepatic encephalopathy (HE) requiring hospitalisation, uncontrolled ascites); (3) high-risk varices not on primary or secondary prevention; (4) recurrent large volume paracentesis (at least two paracenteses in the last 4 weeks); (5) persistent overt HE; (6) cytopenia with platelets <20 000/ μ L, or haemoglobin <80 g/L; (7) altered haemodynamic (heart rate >100 bpm or <50 bpm, systolic blood pressure (BP) >160 mm Hg or <85 mm Hg, diastolic BP >110 mm Hg or <50 mm Hg, oxygen saturation <92% room air); (8) significant heart disease (defined as Canadian Cardiology Society Angina Class III or above, severe aortic stenosis, myocardial infarction in the last month, left ventricular ejection fraction under 50%); (9) awaiting combined organ transplantation; (10) re-transplantation; (11) condition limiting mobilisation and/or exercise; (12) recurrent falls (defined as three falls in the last year).

Study intervention: a multimodal prehabilitation programme

All recruited participants will be offered a supervised prehabilitation programme combining an individualised exercise programme, a detailed nutritional plan and psychological support.

Exercise programme

The exercise programme is led by a team of certified physicians and kinesiologists with experience in prehabilitation. As described later, it is structured as it has a predetermined format, and it is individualised as it is adapted to the capacity of each participant. It is divided into a 4-week induction phase

followed by a 20-week maintenance phase. The duration of the induction and the maintenance phases were developed based on the available literature and considering the average wait time for an LT at our institution. Each session will take place at the MUHC POP complex. The induction phase will include three sessions of 60 min per week for 4 weeks. The maintenance phase will then follow with a 60 min session every other week until the date of surgery or week 24, whichever comes first. Each session will include aerobic and resistance training. The cardiopulmonary exercise testing (CPET) is performed by a certified kinesiologist.¹⁴ Values of workload and VO_2 at peak exercise and anaerobic threshold obtained from CPET will be used to deliver a high-quality individualised exercise programme to each participant. The aerobic exercise is adapted from our own experience using high intensity interval training (HIIT), the latest European society of cardiology guidelines on sports cardiology, and the Morkane study as its preliminary data shows safety and improvement in outcomes using HIIT.^{15–17} The aerobic part will last 28 min: 4 min warm-up, 20 min of HIIT on a stationary bike and 4 min cool-down. The HIIT will consist of four cycles of alternating 3 min of moderate and 2 min of high intensity training. The resistance training follows the aerobic training to complete 60 min. It will include muscle strengthening (shoulders, biceps, triceps, quadriceps, hamstrings, lower leg), flexibility and balance exercises. Muscle strengthening exercises for each muscle group will consist of 1–2 sets of 10 repetitions. Flexibility and balance exercises will consist of 1–2 sets of 2–4 repetitions each. This approach is integrated in the MUHC POP and is recommended by experts.¹³ Increasing levels of difficulty will be allowed for patients that can tolerate it by adding weights based on volitional fatigue. This will help increase their strength week to week without having their muscles adapt to the resistance programme. Patients will also be asked to complete a diary describing physical activity outside of the programmed session that will be reviewed by the kinesiologist. This diary will be included in a patient booklet. Participants will be asked to not consume any alcohol or drugs during study visits, and to adhere to the alcohol and drug policy of the liver transplant service.

Nutritional programme

The nutrition programme is based on current recommendations from the European Association for the Study of Liver and the European Society for Clinical Nutrition and Metabolism.^{18 19} It will be managed by a registered dietitian (RD) with experience in prehabilitation. The primary goal of our nutrition programme is to correct and prevent perioperative malnutrition and support protein anabolism.²⁰ Patients will be assessed by the RD at baseline and categorised based on the Royal Free Hospital-Global Assessment (RFH-GA) tool as adequately nourished,

moderately malnourished and severely malnourished.²¹ Dry weight will be estimated to calculate body mass index (BMI) by correcting for ascites.¹³ In non-obese patients, energy requirements will be estimated using indirect calorimetry and will aim for 1.2–1.4× resting energy expenditure (REE) (approximately 35–40 kcal per kilogram per day of actual body weight). Daily protein requirement will also be estimated using indirect calorimetry, expecting to reach 18%–20% of total calories (approx. 1.2–1.5 g per kg per day of protein of actual body weight). In patients with dry BMI >30 kg/m² (corrected for ascites), energy needs will be estimated at 65% of REE (approximately 25 kcal/kg), with adequate protein intake of 2–2.5 g/kg of ideal body weight, to promote gentle weight loss. For patients with ascites, a diet containing no more than 80 mmol per day of sodium will be recommended. Nutrition interventions will be tailored to each patient's unique nutritional diagnosis and implemented in accordance with patient-identified goals. Additionally, to support exercise-induced anabolism, and an oral nutrition supplement to be consumed immediately after exercise. To determine whether progress has been made towards resolving the nutrition diagnosis and to evaluate that the nutrition prescription is adequately meeting patient needs, patients will be asked to maintain an on paper food recall diary representative of 1 weekend day and 2 weekdays which will be reviewed by the RD for adequacy every 2 weeks. This diary will be included in the patient booklet provided. Patients will also be asked to self-monitor weight. Participants will then receive feedback based on their progress. If a patient fails to meet expected outcomes, the patient will be asked to return for a follow-up visit and re-assessment of their nutrition status and nutrition care plan.

Psychological support programme

Relaxation techniques and coping tools to reduce anxiety related to the upcoming procedure will be provided during a consultation with a clinical nurse specialist who has extensive experience in providing psychological support and coping mechanisms. Consultation includes practice in deep breathing, an introduction to several relaxation strategies, and practice in reframing thoughts toward ones that support a feeling of self-control and are rooted in active coping. Participants will receive a booklet containing tools for self-empowerment and promotion of personal health. Although not formally studied in patients awaiting LT, this psychological support programme was developed jointly with a local expert in such interventions.

Safety of participants

Exercise will be interrupted if certain specific criteria are met as per CPET international standards: angina, symptomatic arrhythmia, fall in systolic BP >20 mm Hg, systolic BP >250 mm Hg or diastolic BP >120 mm Hg, oxygen saturation <80% on room air, loss of coordination, mental confusion, dizziness or faintness.¹⁴ Healthcare workers involved hold advanced cardiac life support certification and access to hospital support. AEs will be assessed by

Table 1 Organisation of study visits

Intervention—Induction phase														
Visits	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14
Week	0	1	1	1	2	2	2	3	3	3	4	4	4	5
Assessments	X													X
CPET	X													X
Assessment of AE		X	X	X	X	X	X	X	X	X	X	X	X	X
Supervised aerobic exercise		X	X	X	X	X	X	X	X	X	X	X		
Supervised resistance training		X	X	X	X	X	X	X	X	X	X	X	X	
RFH-GA	X													X
Nutrition Intervention		X						X						
Stress and anxiety reduction intervention		X						(X)						
Intervention—Maintenance phase							Intervention—Maintenance phase							
Visit number	Visit 15	Visit 16	Visit 17	Visit 18	Visit 19	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 25	Visit 26		
Week	6	8	10	12	14	15	16	18	20	22	24	25		
Assessments						X							X	
CPET					X						X			
Assessment of AE	X	X	X	X	X	X	X	X	X	X	X	X	X	
Supervised aerobic exercise	X	X	X	X			X	X	X	X				
Supervised resistance training	X	X	X	X	X		X	X	X	X	X			
RFH-GA						X						X		
Nutrition Intervention	X						X							
Stress and anxiety reduction intervention	(X)						(X)							

AE, adverse event; CPET, cardiopulmonary exercise testing; RFH-GA, Royal Free Hospital-Global Assessment.

study physician. Incident AEs will be reviewed by the POP team before initiation of exercise. If participant misses a session, they will be contacted to exclude AE. Any serious AE will be reported to the principal investigator within 24 hours and the participant's involvement in the trial suspended until re-assessed.

Duration of the intervention

The intervention is divided into a 4-week induction phase followed by a 20-week maintenance phase. There will be assessment visits at the end of the induction phase, midway through the maintenance phase and at the end of the maintenance phase (table 1). The prehabilitation programme will end after 24 weeks of study visits, if the participant undergoes LT, if an AE leads to discontinuation of the intervention or if a participant meets

an exclusion criteria during study participation. The latter can happen as patients on the liver transplant list can have progression of liver disease while waiting for transplantation.

Study visits

Patients are screened at the liver transplant clinic of the MUHC. After review of selection criteria, those that agree to participate will sign the ICF and receive a unique participant identifier (ID). Potential participants who meet all eligibility criteria but refuse to participate will be asked by their treating hepatologist the reason for their refusal to participate. This information will be collected and transmitted to the study team. At the second visit, participants who agreed to participate and signed the ICF undergo a formal evaluation of their exercise and nutritional status

at the POP complex. Participants are expected to come to the POP complex as per above intervention protocol. At each study visit, a history, physical examination, review of laboratory values and assessment of AE will be performed. Study-related data will also be collected. Study visits are summarised in [table 1](#).

Study outcomes definition

Primary objective: feasibility

Feasibility is defined as being able to recruit 25 participants, have a protocol adherence above 70%, and LTFU below 15%. Adherence to the protocol will refer to the proportion of recruited patients that attend 70% of scheduled supervised exercise sessions. Although there is no standardised definition to determine feasibility, achieving the above criteria would be in-line with studies performed in this clinical context.^{15 22 23} In addition, a publication from the POP group over a 5-year period of time reports an adherence of 70%–98% with the protocol and an LTFU of 14%.²⁴

Secondary objective: safety

To evaluate the safety of our intervention, we will record all AEs from recruitment until withdrawal from study, or date of surgery to limit selective outcome reporting bias. We will follow the Common Terminology Criteria for AEs version 5.0 for grading and reporting AEs.²⁵ AEs will be categorised as related to the intervention or not as assessed by a study physician. Serious AEs will be defined as any AE that leads to hospitalisation or death. We will also identify AEs associated with temporary or permanent interruption of the intervention. Our intervention will be considered safe if there are 5% or less serious AEs related to our intervention.

Exploratory objectives: effectiveness of the intervention

We will capture a broad range of metrics influenced by our intervention based on previous studies.¹² As this is a novel intervention in patients with cirrhosis, the magnitude of change between baseline and follow-up necessary to derive a definite clinical benefit is unclear. For this reason, a positive effect will be defined as any improvement in baseline values compared with the last pre-liver transplant values as assessed by statistical means. For frailty, we will monitor for change in liver frailty index (LFI) and proportion of frail individuals. A 0.1 change in LFI is clinically significant.⁷ For exercise capacity, 6-minute walk test (6MWT), Metabolic Equivalent of Task (MET), peak workload, peak VO_2 will be assessed. A 14–30 m change in 6MWT, a 6% increase in peak VO_2 or a 1.0 mL/kg/min change in peak VO_2 are considered clinically significant, but this is not validated in cirrhosis.^{26 27} For muscle mass and strength, we will assess change in Hand Grip Strength (HGS). Malnutrition will be assessed by a change in RFH-GA class or a change in proportion of severely malnourished individuals. Interval improvement in Chronic Liver Disease Questionnaire (CLDQ) will confirm the positive impact of our programme on

HRQoL. We will assess delisting due to death or being too unwell.

We will capture postoperative outcomes that might improve following prehabilitation. The type, frequency and severity of complications will be recorded and summarised using the Comprehensive Complication Index (CCI).²⁸ We will also record hospital LOS in days, non-home discharge (home vs not home), re-admission and mortality at 3 months and 12 months.

Data collection

We will record baseline age, sex, gender, smoking status, alcohol consumption status, history of diabetes, aetiology of liver disease, albumin, bilirubin, international normalised ratio, ascites, HE, creatinine, sodium, presence of hepatocellular carcinoma, history and type of decompensated liver disease (varices, ascites, HE), history of cardiovascular disease, and history of dyslipidaemia at initial visit. Reason for refusal to participate in the study will be collected by the treating hepatologist and transmitted to the research team to avoid contacting participants who have refused to participate. Research personnel will record reason for lack of protocol adherence and LTFU. At baseline, and at prespecified visits during the intervention, LFI, peak VO_2 , peak workload, METS, 6MWT, HGS, RFH-GA, BMI and CLDQ will be recorded by the research personnel. Participant diary will be reviewed with the kinesiologist and dietician and respective data entered accordingly. AEs will be recorded. HGS will be measured using a handheld dynamometer. Research personnel will follow patients throughout their time in the prehabilitation programme and during their hospital course recording all data and outcomes as set out in the aims above. Research personnel will review participant data at each study visit for new events. Mortality at 3 months and 12 months will be assessed through chart review, and contacting participant if necessary. If an outcome has occurred, the study team will obtain the appropriate documentation. All patient data will be coded. Study personnel will submit the trial data by completing the Case Report Forms through a secure web-based password protected data collection programme (RedCAP). Source documentation supporting the trial will be made available for trial related monitoring, audits and institutional ethics review.

Statistical analysis

To address the feasibility objective, we will report recruitment, adherence, LTFU, study withdrawal as frequencies (percentages). Reasons for the following will be recorded: refusal to participate in eligible patients, lack of adherence, LTFU and study withdrawal. Reasons will be categorised and reported as proportion (percentages). To address the safety objective, we will report AEs as event frequency per-type, and per-patient. We will separately report and describe serious AEs related to the intervention. To assess the impact of our intervention, we will perform this analysis in all recruited patients. We will

also perform a separate analysis for those that adhered and those that did not adhere to protocol. We will report LFI, 6MWT, peak $\text{VO}_{2\text{p}}$, peak workload, METS, HGS, RFH-GA, CLDQ as continuous variables using means (SD) or medians (IQR). We will report the frequency (percentage) of frail patients and severely malnourished patients. The variables will be presented at baseline and at prespecified visits before LT. Paired data (before/after) will be compared using Wilcoxon signed-rank test analysis for continuous variables without normal distribution, t-test for continuous variables with normal distribution, and Fisher's exact for categorical variables. To account for the variability in follow-up, the protocol was developed in a way to have multiple assessment time points throughout the study. Patients will be assessed based on the number of assessment visit completed. The frequency (%) of patients delisted due to death or being too unwell will be reported. To assess the impact of our intervention on postoperative outcomes, we will perform this analysis on the subgroup of patients that underwent LT. We will also separately assess postoperative outcomes in patients that have adhered and those that have not adhered to our protocol. We will report the type, frequency and severity of complications, CCI, LOS, and re-admissions at 3 months as continuous variables using means (SD) and medians (IQR). Non-home discharge and death at 3 months and 12 months will be reported as frequency (%). Where applicable, 95% CI will be reported. All p values are two-tailed, and values <0.05 will be considered statistically significant. Analyses will be performed using SPSS (V.24.0). Reporting will be in accordance with the Consolidated Standards of Reporting Trials guidance for non-randomised feasibility studies.^{22 29}

Sample size and timeline

Due to the feasibility nature of the proposed trial, we propose a convenient sample size of 25 participants using currently available literature.^{15 23 30} As this is a feasibility study with potential unforeseen obstacles, we expect 30 months to finalise recruitment and completion of the study visits.

Patient and public involvement

Patient and public were not involved in the design, or the conduct of this study. There currently is no plan for them to be involved in the reporting or dissemination plans of the research.

ETHICS AND DISSEMINATION

This study is approved by the Research Institute of the MUHC (2021-7646). Safety of participants is of utmost importance. Protocol development has focused on ensuring the intervention is safe. AEs will also be monitored by the trial team before each visit during the duration of the study. In terms of dissemination plans, we will submit our findings for conference presentation at the CDTRP and the CASL annual scientific meetings. We will

submit our findings at international conferences on hepatology (eg, Liver Meeting of the American Association for the Study of Liver Diseases, and the International Liver Congress of the European Association for the Study of the Liver) and on perioperative medicine. Our findings will be submitted in a peer-reviewed journal with open access to facilitate dissemination.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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REFERENCES

- Lai JC, Feng S, Terrault NA, *et al*. Frailty predicts waitlist mortality in liver transplant candidates. *Am J Transplant* 2014;14:1870–9.
- Merli M, Berzigotti A, Zelber-Sagi S, *et al*. EASL clinical practice guidelines on nutrition in chronic liver disease. *J Hepatol* 2019;70:172–93.
- Tapper EB, Konerman M, Murphy S, *et al*. Hepatic encephalopathy impacts the predictive value of the fried frailty index. *Am J Transplant* 2018;18:2566–70.
- Tandon P, Low G, Mourtzakis M, *et al*. A model to identify sarcopenia in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2016;14:1473–80.
- Lai JC, Covinsky KE, McCulloch CE, *et al*. The liver frailty index improves mortality prediction of the subjective clinician assessment in patients with cirrhosis. *Am J Gastroenterol* 2018;113:235–42.
- Lai JC, Rahimi RS, Verna EC, *et al*. Frailty associated with waitlist mortality independent of ascites and hepatic encephalopathy in a multicenter study. *Gastroenterology* 2019;156:1675–82.
- Lai JC, Dodge JL, Kappus MR, *et al*. Changes in frailty are associated with waitlist mortality in patients with cirrhosis. *J Hepatol* 2020;73:575–81.

- 8 Lai JC, Segev DL, McCulloch CE, *et al.* Physical frailty after liver transplantation. *Am J Transplant* 2018;18:1986–94.
- 9 Richards SJG, Frizelle FA, Geddes JA, *et al.* Frailty in surgical patients. *Int J Colorectal Dis* 2018;33:1657–66.
- 10 Panayi AC, Orkaby AR, Sakthivel D, *et al.* Impact of frailty on outcomes in surgical patients: a systematic review and meta-analysis. *Am J Surg* 2019;218:393–400.
- 11 Negm AM, Kennedy CC, Thabane L, *et al.* Management of frailty: a systematic review and network meta-analysis of randomized controlled trials. *J Am Med Dir Assoc* 2019;20:1190–8.
- 12 Williams FR, Berzigotti A, Lord JM, *et al.* Review article: impact of exercise on physical frailty in patients with chronic liver disease. *Aliment Pharmacol Ther* 2019;50:988–1000.
- 13 Tandon P, Ismond KP, Riess K, *et al.* Exercise in cirrhosis: translating evidence and experience to practice. *J Hepatol* 2018;69:1164–77.
- 14 Levett DZH, Jack S, Swart M, *et al.* Perioperative cardiopulmonary exercise testing (CPET): consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. *Br J Anaesth* 2018;120:484–500.
- 15 Morkane CM, Kearney O, Bruce DA, *et al.* An outpatient hospital-based exercise training program for patients with cirrhotic liver disease awaiting transplantation: a feasibility trial. *Transplantation* 2020;104:97–103.
- 16 Minnella EM, Ferreira V, Awasthi R, *et al.* Effect of two different pre-operative exercise training regimens before colorectal surgery on functional capacity: a randomised controlled trial. *Eur J Anaesthesiol* 2020;37:969–78.
- 17 Pelliccia A, Sharma S, Gati S, *et al.* ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2020.
- 18 European Association for the Study of the Liver. EASL clinical practice guidelines on nutrition in chronic liver disease. *J Hepatol* 2019;70:172–93.
- 19 Plauth M, Bernal W, Dasarthy S, *et al.* ESPEN guideline on clinical nutrition in liver disease. *Clin Nutr* 2019;38:485–521.
- 20 Gillis C, Wischmeyer PE. Pre-operative nutrition and the elective surgical patient: why, how and what *Anaesthesia* 2019;74 Suppl 1:27–35.
- 21 Morgan MY, Madden AM, Soulsby CT, *et al.* Derivation and validation of a new global method for assessing nutritional status in patients with cirrhosis. *Hepatology* 2006;44:823–35.
- 22 Eldridge SM, Chan CL, Campbell MJ, *et al.* CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ* 2016;355:i2339.
- 23 Williams FR, Vallance A, Faulkner T, *et al.* Home-based exercise in patients awaiting liver transplantation: A feasibility study. *Liver Transpl* 2019;25:995–1006.
- 24 Minnella EM, Bousquet-Dion G, Awasthi R, *et al.* Multimodal prehabilitation improves functional capacity before and after colorectal surgery for cancer: a five-year research experience. *Acta Oncol* 2017;56:295–300.
- 25 Institute NC. Common terminology criteria for adverse events (CTCAE) version 5.0, 2017. Available: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf
- 26 Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. *J Eval Clin Pract* 2017;23:377–81.
- 27 Swank AM, Horton J, Fleg JL, *et al.* Modest increase in peak Vo2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. *Circ Heart Fail* 2012;5:579–85.
- 28 Slankamenac K, Graf R, Barkun J, *et al.* The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Ann Surg* 2013;258:1–7.
- 29 Lancaster GA, Thabane L. Guidelines for reporting non-randomised pilot and feasibility studies. *Pilot Feasibility Stud* 2019;5:114.
- 30 Debette-Gratien M, Tabouret T, Antonini M-T, *et al.* Personalized adapted physical activity before liver transplantation: acceptability and results. *Transplantation* 2015;99:145–50.