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

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Manuscripts

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3 **Prehabilitation in patients with cirrhosis awaiting liver transplantation: protocol of a**
4 **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 program 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 program conducted at the PeriOperative Program complex of the MUHC. It includes exercise training with a certified kinesiologist (aerobic and resistance training), nutritional optimization with a registered dietician, and psychological support with a nurse specialist. The exercise training program is divided into an induction phase with 3 sessions per week for 4 weeks followed by a maintenance phase with 1 session every other week for 20 weeks. Aerobic training will be individualized based on result from cardiopulmonary exercise testing 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.

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3 **Ethics and dissemination**
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5 The research ethics board of the MUHC has approved this study (2021-7646). Our findings will
6 be submitted for presentation at national and international conferences, and for peer-reviewed
7 publication.
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12 **Registration:** clinicaltrials.gov (NCT05237583)
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For peer review only

STRENGTH AND LIMITATIONS OF THIS STUDY

- The feasibility, safety, and effectiveness of a multimodal prehabilitation program in patients with cirrhosis awaiting liver transplantation is unknown.
- The PeriOperative Program clinic of the McGill University has tremendous experience in leading prehabilitation clinical trials.
- This carefully planned supervised multimodal prehabilitation will include exercise training, nutritional optimization, 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 multicenter randomized controlled trial to specifically isolate the impact of prehabilitation in this patient population.

INTRODUCTION

Frailty has emerged as a major predictor of worse outcome in patients with cirrhosis(1). It is defined as a decreased physiologic 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, respectively(3-5). The presence of frailty is independently associated with waitlist mortality, while worsening frailty also predicts increased pre-transplant mortality(6, 7). Pre-transplant 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 post-operative mortality, and doubles the risk of major complications, re-operation, failed discharge, and re-admission to hospital(10). A network meta-analysis of 5,262 participants in randomized controlled trials (RCT) 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 prehabilitation combining exercise training, nutritional optimization and psychological support, in patients with cirrhosis awaiting liver transplantation 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 prehabilitation program. Second, it will determine if the prehabilitation program can improve key preoperative markers of frailty. Lastly, it will describe postoperative outcomes in those that underwent liver transplantation.

STUDY OBJECTIVES

Primary objective: Feasibility

The primary objective of this study is to determine if it is feasible for patients with cirrhosis awaiting liver transplantation to participate in a multimodal prehabilitation program combining exercise, nutritional optimization and psychological support. To determine feasibility, we will: i) assess the proportion of patients on the liver transplant list that would be eligible to participate in our study; ii) assess the proportion of eligible participants that are recruited into the study; iii) assess protocol adherence and loss to follow-up (LTFU) following study entry; iv) 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 liver transplantation to participate in a multimodal prehabilitation program. For this, we will determine the incidence of serious and non-serious adverse events (AE) during participation in the study, based on the Common Terminology Criteria for AEs v5.0 classification⁶².

Exploratory objectives: Effectiveness of the intervention

The exploratory aims will evaluate if our multimodal prehabilitation program 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 liver transplantation

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 program if they agree to be contacted by the study team. The prehabilitation program will be conducted at the PeriOperative Program (POP) complex. This study is approved by the MUHC Research Ethics Board (study ID 2021-7646) and is registered on clinicaltrials.gov (NCT05237583).

Inclusion criteria

Patients with the following characteristics will be assessed for inclusion into the study: i) age above 18 years; ii) diagnosis of cirrhosis, based on clinical, laboratory, imaging, or histology findings; iii) active on the liver transplant waiting list of the MUHC; iv) 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 include(13): i) MELD >20; ii) Hepatic decompensation within the last month (defined as variceal bleed, overt hepatic encephalopathy (HE) requiring hospitalization, uncontrolled ascites); iii) High risk varices not on primary or secondary prevention; iv) Recurrent large volume paracentesis (at least two paracenteses in the last 4 weeks); v) Persistent HE; vi) Cytopenia with platelets <20,000/ μ L, or hemoglobin <80g/L; vii) Altered hemodynamics (heart rate >100bpm or <50bpm, systolic blood pressure (BP) >160mmHg or <85mmHg, diastolic BP >110mmHg or <50mmHg, oxygen saturation <92% room air); viii) 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%); ix) Awaiting combined organ

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3 transplantation; x) Re-transplantation; xi) Condition limiting mobilization and/or exercise; xii)
4 Recurrent falls (defined as 3 falls in the last year).
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8 **Study intervention: a multimodal prehabilitation program**

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10 All recruited participants will be offered a supervised prehabilitation program combining an
11 individualized exercise program, a detailed nutritional plan, and psychological support.
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15 *Exercise program*

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17 The exercise program is led by a team of certified physicians and kinesiologists with experience
18 in prehabilitation. As shown below, it is structured as it has a predetermined format, and it is
19 individualized as it is adapted to the capacity of each participant. It is divided into a 4-week
20 induction phase followed by a 20-week maintenance phase. The duration of the induction and
21 the maintenance phases were developed based on the available literature and considering the
22 average wait time for a liver transplantation at our institution. Each session will take place at the
23 MUHC POP complex. The induction phase will include 3 sessions of 60 minutes (mins) per week
24 for 4 weeks. The maintenance phase will then follow with a 60 mins session every other week
25 until the date of surgery or week 24, whichever comes first. Each session will include aerobic and
26 resistance training. The cardiopulmonary exercise testing (CPET) is performed by a certified
27 kinesiologist(14). Values of workload and VO_2 at peak exercise and anaerobic threshold (AT)
28 obtained from CPET will be used to deliver a high-quality individualized exercise program to each
29 participant. The aerobic exercise is adapted from our own experience using high intensity interval
30 training (HIIT), the latest European society of cardiology guidelines on sports cardiology, and the
31 Morkane study as its preliminary data shows safety and improvement in outcomes using HIIT(15-
32 17). The aerobic part will last 28 mins: 4 mins warm-up, 20 mins of HIIT on a stationary bike, and
33 4 mins cool-down. The HIIT will consist of 4 cycles of alternating 3 mins of moderate and 2 mins
34 of high intensity training. The resistance training follows the aerobic training to complete 60
35 mins. It will include muscle strengthening (shoulders, biceps, triceps, quadriceps, hamstrings,
36 lower leg), flexibility, and balance exercises. Muscle strengthening exercises for each muscle
37 group will consist of 1-2 sets of 10 repetitions. Flexibility and balance exercises will consist of 1-
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3 2 sets of 2-4 repetitions each. This approach is integrated in the MUHC POP and is recommended
4 by experts(13). Increasing levels of difficulty will be allowed for patients that can tolerate it by
5 adding weights based on volitional fatigue. This will help increase their strength week to week
6 without having their muscles adapt to the resistance program. Patients will also be asked to
7 complete a diary describing physical activity outside of the programmed session that will be
8 reviewed by the kinesiologist. This diary will be included in a patient booklet. Participants will be
9 asked to not consume any alcohol or drugs during study visits, and to adhere to the alcohol and
10 drug policy of the liver transplant service.
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20 *Nutritional program*

21 The nutrition program is based on current recommendations from the European Association for
22 the Study of Liver and the European Society for Clinical Nutrition and Metabolism(18, 19). It will
23 be managed by a registered dietitian (RD) with experience in prehabilitation. The primary goal of
24 our nutrition program is to correct and prevent perioperative malnutrition and support protein
25 anabolism(20). Patients will be assessed by the RD at baseline and categorized based on the Royal
26 Free Hospital-Global Assessment (RFH-GA) tool as adequately nourished, moderately
27 malnourished and severely malnourished(21). Dry weight will be estimated to calculate body
28 mass index (BMI) by correcting for ascites(13). In non-obese patients, energy requirements will
29 be estimated using indirect calorimetry and will aim for 1.2-1.4x resting energy expenditure (REE)
30 (approximately 35-40 kcal per kilogram per day of actual body weight). Daily protein requirement
31 will also be estimated using indirect calorimetry, expecting to reach 18-20% of total calories
32 (approx. 1.2-1.5g per kg per day of protein of actual body weight). In patients with dry BMI >
33 30kg/m² (corrected for ascites), energy needs will be estimated at 65% of REE (approximately
34 25kcal/kg), with adequate protein intake of 2-2.5g/kg of ideal body weight, to promote gentle
35 weight loss. For patients with ascites, a diet containing no more than 80mmol per day of sodium
36 will be recommended. Nutrition interventions will be tailored to each patient's unique nutritional
37 diagnosis and implemented in accordance with patient-identified goals. Additionally, to support
38 exercise-induced anabolism, and an oral nutrition supplement to be consumed immediately after
39 exercise. To determine whether progress has been made towards resolving the nutrition
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3 diagnosis and to evaluate that the nutrition prescription is adequately meeting patient needs,
4 patients will be asked to maintain an on paper food recall diary representative of 1 weekend day
5 and 2 weekdays which will be reviewed by the RD for adequacy every two weeks. This diary will
6 be included in the patient booklet provided. Patients will also be asked to self-monitor weight.
7 Participants will then receive feedback based on their progress. If a patient fails to meet expected
8 outcomes, the patient will be asked to return for a follow-up visit and re-assessment of their
9 nutrition status and nutrition care plan.
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16 17 18 *Psychological support program*

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

37 Exercise will be interrupted if certain specific criteria are met as per CPET international standards:
38 angina, symptomatic arrhythmia, fall in systolic BP >20mmHg, systolic BP >250mmHg or diastolic
39 BP >120mmHg, oxygen saturation <80% on room air, loss of coordination, mental confusion,
40 dizziness or faintness(14). Healthcare workers involved hold advanced cardiac life support
41 certification and access to hospital support. AEs will be assessed by study physician. Incident AEs
42 will be reviewed by the POP team before initiation of exercise. If participant misses a session,
43 they will be contacted to exclude AE. Any serious AE will be reported to the principal investigator
44 within 24 hours and the participant's involvement in the trial suspended until re-assessed.
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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, mid-way through the maintenance phase, and at the end of the maintenance phase (Table 1). The prehabilitation program will end after 24 weeks of study visits, if the participant undergoes liver transplantation, 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 exam, review of laboratory values and assessment of AE will be performed. Study-related data will also be collected as per the description below. Study visits are summarized 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 standardized 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

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3 group over a 5-year period of time reports an adherence of 70 to 98 % with the protocol and a
4 LTFU of 14%(24).
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9 *Secondary objective: Safety*

10 To evaluate the safety of our intervention, we will record all AEs from recruitment until
11 withdrawal from study, or date of surgery to limit selective outcome reporting bias. We will
12 follow the Common Terminology Criteria for AEs v5.0 for grading and reporting AEs(25). AEs will
13 be categorized as related to the intervention or not as assessed by a study physician. Serious AEs
14 will be defined as any AE that leads to hospitalization or death. We will also identify AEs
15 associated with temporary or permanent interruption of the intervention. Our intervention will
16 be considered safe if there are 5% or less serious AEs related to our intervention.
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25 *Exploratory objectives: Effectiveness of the intervention*

26 We will capture a broad range of metrics influenced by our intervention based on previous
27 studies(12). As this is a novel intervention in patients with cirrhosis, the magnitude of change
28 between baseline and follow-up necessary to derive a definite clinical benefit is unclear. For this
29 reason, a positive effect will be defined as any improvement in baseline values compared to the
30 last pre-liver transplant values as assessed by statistical means. For frailty, we will monitor for
31 change in LFI and proportion of frail individuals. A 0.1 change in LFI is clinically significant(7). For
32 exercise capacity, 6MWT, METS, peak workload, peak VO₂ will be assessed. A 14 to 30m change
33 in 6MWT, a 6% increase in peak VO₂ or a 1.0mL/kg/min change in peak VO₂ are considered
34 clinically significant, but this is not validated in cirrhosis(26, 27). For muscle mass and strength,
35 we will assess change in HGS. Malnutrition will be assessed by a change in RFH-GA class or a
36 change in proportion of severely malnourished individuals. Interval improvement in CLDQ will
37 confirm the positive impact of our program on HRQoL. We will assess delisting due to death or
38 being too unwell.
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52 We will capture postoperative outcomes that might improve following prehabilitation. The type,
53 frequency, and severity of complications will be recorded and summarized using the CCI(28). We
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3 will also record hospital LOS in days, non-home discharge (home vs not home), re-admission and
4 mortality at 3- and 12-months.
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8 9 **Data collection**

10 We will record baseline age, sex, gender, smoking status, alcohol consumption status, history of
11 diabetes, etiology of liver disease, albumin, bilirubin, INR, ascites, HE, creatinine, sodium,
12 presence of HCC, history and type of decompensated liver disease (varices, ascites, HE), history
13 of cardiovascular disease, and history of dyslipidemia at initial visit. Reason for refusal to
14 participate in the study will be collected by the treating hepatologist and transmitted to the
15 research team to avoid contacting participants who have refused to participate. Research
16 personnel will record reason for lack of protocol adherence and LTFU. At baseline, and at pre-
17 specified visits during the intervention, LFI, peak VO₂, peak workload, METS, 6MWT, HGS, RFH-
18 GA, BMI, and CLDQ will be recorded by the research personnel. Participant diary will be reviewed
19 with the kinesiologist and dietician and respective data entered accordingly. AEs will be recorded
20 as per above. HGS will be measured using a handheld dynamometer. Research personnel will
21 follow patients throughout their time in the prehabilitation program and during their hospital
22 course recording all data and outcomes as set out in the aims above. Research personnel will
23 review participant data at each study visit for new events. Mortality at 3- and 12-months will be
24 assessed through chart review, and contacting participant if necessary. If an outcome has
25 occurred, the study team will obtain the appropriate documentation. All patient data will be
26 coded. Study personnel will submit the trial data by completing the Case Report Forms through
27 a secure web-based password protected data collection program (RedCAP). Source
28 documentation supporting the trial will be made available for trial related monitoring, audits,
29 and institutional ethics review.
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49 **Statistical analysis**

50 To address the feasibility objective, we will report recruitment, adherence, LTFU, study
51 withdrawal as frequencies (percentages). Reasons for the following will be recorded: refusal to
52 participate in eligible patients, lack of adherence, LTFU, and study withdrawal. Reasons will be
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3 categorized and reported as proportion (percentages). To address the safety objective, we will
4 report AEs as event frequency per-type, and per-patient. We will separately report and describe
5 serious AEs related to the intervention. To assess the impact of our intervention, we will perform
6 this analysis in all recruited patients. We will also perform a separate analysis for those that
7 adhered and those that did not adhere to protocol. We will report LFI, 6MWT, peak VO₂, peak
8 workload, METS, HGS, RFH-GA, CLDQ as continuous variables using means (SD) or medians (IQR).
9 We will report the frequency (percentage [%]) of frail patients and severely malnourished
10 patients. The variables will be presented at baseline and at pre-specified visits before liver
11 transplantation. Paired data (before/after) will be compared using Wilcoxon Signed Rank Test
12 analysis for continuous variables without normal distribution, t-test for continuous variables with
13 normal distribution, and Fisher's exact for categorical variables. To account for the variability in
14 follow-up, the protocol was developed in a way to have multiple assessment time points
15 throughout the study. Patients will be assessed based on the number of assessment visit
16 completed. The frequency (%) of patients delisted due to death or being too unwell will be
17 reported. To assess the impact of our intervention on postoperative outcomes, we will perform
18 this analysis on the sub-group of patients that underwent liver transplantation. We will also
19 separately assess postoperative outcomes in patients that have adhered and those that have not
20 adhered to our protocol. We will report the type, frequency, and severity of complications, CCI,
21 LOS, and re-admissions at 3-months as continuous variables using means (SD) and medians (IQR).
22 Non-home discharge and death at 3- and 12-months will be reported as frequency (%). Where
23 applicable, 95% CI will be reported. All p-values are two-tailed, and values <0.05 will be
24 considered statistically significant. Analyses will be performed using SPSS (v24.0). Reporting will
25 be in accordance with the CONSORT guidance for non-randomized feasibility studies(22, 29).
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47 **Sample size and timeline**

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49 Due to the feasibility nature of the proposed trial, we propose a convenient sample size of 25
50 participants using currently available literature(15, 23, 30). As this is a feasibility study with
51 potential unforeseen obstacles, we expect 30 months to finalize recruitment and completion of
52 the study visits.
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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. Adverse events 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 (example: 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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AUTHORS' CONTRIBUTIONS

All authors listed have significantly contributed to the conceptualization and design of this study directed by Dr. Amine Benmassaoud, Dr. Franco Carli and Dr. Amal Bessissow. In addition, Dr. Chelsia Gillis contributed her expertise to the nutritional intervention, Rashami Awasthi to the exercise program, Linda Edgar to the psychological support program, Myriam Martel to the statistical analysis, and Dr. Jeffrey Barkun, Dr. Tianyan Chen, and Dr. Giada Sebastiani to the pre-and post-transplant considerations.

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COMPETING INTEREST STATEMENT

All others have no competing interests to declare for this study.

Table 1. Organization 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
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)					

BMJ Open

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

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Manuscripts

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3 **Prehabilitation in patients with cirrhosis awaiting liver transplantation: protocol of a**
4 **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 program 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 program conducted at the PeriOperative Program complex of the MUHC. It includes exercise training with a certified kinesiologist (aerobic and resistance training), nutritional optimization with a registered dietician, and psychological support with a nurse specialist. The exercise training program is divided into an induction phase with 3 sessions per week for 4 weeks followed by a maintenance phase with 1 session every other week for 20 weeks. Aerobic training will be individualized based on result from cardiopulmonary exercise testing 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.

Registration: clinicaltrials.gov (NCT05237583)

First posted on clinicaltrials.gov: February 14, 2022

Actual study start (first participant recruited): February 23, 2022

Expected date of study completion: October 2024

STRENGTH AND LIMITATIONS OF THIS STUDY

- The feasibility, safety, and effectiveness of a multimodal prehabilitation program in patients with cirrhosis awaiting liver transplantation is unknown.
- The PeriOperative Program clinic of the McGill University has tremendous experience in leading prehabilitation clinical trials.
- This carefully planned supervised multimodal prehabilitation will include exercise training, nutritional optimization, 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 randomized controlled trial to specifically isolate the impact of prehabilitation in this patient population.

INTRODUCTION

Frailty has emerged as a major predictor of worse outcome in patients with cirrhosis(1). It is defined as a decreased physiologic 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, respectively(3-5). The presence of frailty is independently associated with waitlist mortality, while worsening frailty also predicts increased pre-transplant mortality(6, 7). Pre-transplant 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 post-operative mortality, and doubles the risk of major complications, re-operation, failed discharge, and re-admission to hospital(10). A network meta-analysis of 5,262 participants in randomized controlled trials (RCT) 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 optimization and psychological support, in patients with cirrhosis awaiting liver transplantation 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 program. Second, it will determine if the prehabilitation program can improve key preoperative markers of frailty. Lastly, it will describe postoperative outcomes in those that underwent liver transplantation.

STUDY OBJECTIVES

Primary objective: Feasibility

The primary objective of this study is to determine if it is feasible for patients with cirrhosis awaiting liver transplantation to participate in a multimodal prehabilitation program combining exercise, nutritional optimization and psychological support. To determine feasibility, we will: i) assess the proportion of patients on the liver transplant list that would be eligible to participate in our study; ii) assess the proportion of eligible participants that are recruited into the study; iii) assess protocol adherence and loss to follow-up (LTFU) following study entry; iv) 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 liver transplantation to participate in a multimodal prehabilitation program. For this, we will determine the incidence of serious and non-serious adverse events (AE) during participation in the study, based on the Common Terminology Criteria for AEs v5.0 classification⁶².

Exploratory objectives: Effectiveness of the intervention

The exploratory aims will evaluate if our multimodal prehabilitation program 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 liver transplantation

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 program if they agree to be contacted by the study team. The prehabilitation program will be conducted at the PeriOperative Program (POP) complex. This study is approved by the MUHC Research Ethics Board (study ID 2021-7646) and is registered on clinicaltrials.gov (NCT05237583).

Inclusion criteria

Patients with the following characteristics will be assessed for inclusion into the study: i) age above 18 years; ii) diagnosis of cirrhosis, based on clinical, laboratory, imaging, or histology findings; iii) active on the liver transplant waiting list of the MUHC; iv) 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 include(13): i) MELD >20; ii) Acute hepatic decompensation within the last month (defined as variceal bleed, overt hepatic encephalopathy (HE) requiring hospitalization, uncontrolled ascites); iii) High risk varices not on primary or secondary prevention; iv) Recurrent large volume paracentesis (at least two paracenteses in the last 4 weeks); v) Persistent overt HE; vi) Cytopenia with platelets <20,000/ μ L, or haemoglobin <80g/L; vii) Altered hemodynamic (heart rate >100bpm or <50bpm, systolic blood pressure (BP) >160mmHg or <85mmHg, diastolic BP >110mmHg or <50mmHg, oxygen saturation <92% room air); viii) 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%); ix) Awaiting

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3 combined organ transplantation; x) Re-transplantation; xi) Condition limiting mobilization and/or
4 exercise; xii) Recurrent falls (defined as 3 falls in the last year).
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8 **Study intervention: a multimodal prehabilitation program**

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10 All recruited participants will be offered a supervised prehabilitation program combining an
11 individualized exercise program, a detailed nutritional plan, and psychological support.
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15 *Exercise program*

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17 The exercise program is led by a team of certified physicians and kinesiologists with experience
18 in prehabilitation. As shown below, it is structured as it has a predetermined format, and it is
19 individualized as it is adapted to the capacity of each participant. It is divided into a 4-week
20 induction phase followed by a 20-week maintenance phase. The duration of the induction and
21 the maintenance phases were developed based on the available literature and considering the
22 average wait time for a liver transplantation at our institution. Each session will take place at the
23 MUHC POP complex. The induction phase will include 3 sessions of 60 minutes (mins) per week
24 for 4 weeks. The maintenance phase will then follow with a 60 mins session every other week
25 until the date of surgery or week 24, whichever comes first. Each session will include aerobic and
26 resistance training. The cardiopulmonary exercise testing (CPET) is performed by a certified
27 kinesiologist(14). Values of workload and VO_2 at peak exercise and anaerobic threshold (AT)
28 obtained from CPET will be used to deliver a high-quality individualized exercise program to each
29 participant. The aerobic exercise is adapted from our own experience using high intensity interval
30 training (HIIT), the latest European society of cardiology guidelines on sports cardiology, and the
31 Morkane study as its preliminary data shows safety and improvement in outcomes using HIIT(15-
32 17). The aerobic part will last 28 mins: 4 mins warm-up, 20 mins of HIIT on a stationary bike, and
33 4 mins cool-down. The HIIT will consist of 4 cycles of alternating 3 mins of moderate and 2 mins
34 of high intensity training. The resistance training follows the aerobic training to complete 60
35 mins. It will include muscle strengthening (shoulders, biceps, triceps, quadriceps, hamstrings,
36 lower leg), flexibility, and balance exercises. Muscle strengthening exercises for each muscle
37 group will consist of 1-2 sets of 10 repetitions. Flexibility and balance exercises will consist of 1-
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3 2 sets of 2-4 repetitions each. This approach is integrated in the MUHC POP and is recommended
4 by experts(13). Increasing levels of difficulty will be allowed for patients that can tolerate it by
5 adding weights based on volitional fatigue. This will help increase their strength week to week
6 without having their muscles adapt to the resistance program. Patients will also be asked to
7 complete a diary describing physical activity outside of the programmed session that will be
8 reviewed by the kinesiologist. This diary will be included in a patient booklet. Participants will be
9 asked to not consume any alcohol or drugs during study visits, and to adhere to the alcohol and
10 drug policy of the liver transplant service.
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20 *Nutritional program*

21 The nutrition program is based on current recommendations from the European Association for
22 the Study of Liver and the European Society for Clinical Nutrition and Metabolism(18, 19). It will
23 be managed by a registered dietitian (RD) with experience in prehabilitation. The primary goal of
24 our nutrition program is to correct and prevent perioperative malnutrition and support protein
25 anabolism(20). Patients will be assessed by the RD at baseline and categorized based on the Royal
26 Free Hospital-Global Assessment (RFH-GA) tool as adequately nourished, moderately
27 malnourished and severely malnourished(21). Dry weight will be estimated to calculate body
28 mass index (BMI) by correcting for ascites(13). In non-obese patients, energy requirements will
29 be estimated using indirect calorimetry and will aim for 1.2-1.4x resting energy expenditure (REE)
30 (approximately 35-40 kcal per kilogram per day of actual body weight). Daily protein requirement
31 will also be estimated using indirect calorimetry, expecting to reach 18-20% of total calories
32 (approx. 1.2-1.5g per kg per day of protein of actual body weight). In patients with dry BMI >
33 30kg/m² (corrected for ascites), energy needs will be estimated at 65% of REE (approximately
34 25kcal/kg), with adequate protein intake of 2-2.5g/kg of ideal body weight, to promote gentle
35 weight loss. For patients with ascites, a diet containing no more than 80mmol per day of sodium
36 will be recommended. Nutrition interventions will be tailored to each patient's unique nutritional
37 diagnosis and implemented in accordance with patient-identified goals. Additionally, to support
38 exercise-induced anabolism, and an oral nutrition supplement to be consumed immediately after
39 exercise. To determine whether progress has been made towards resolving the nutrition
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3 diagnosis and to evaluate that the nutrition prescription is adequately meeting patient needs,
4 patients will be asked to maintain an on paper food recall diary representative of 1 weekend day
5 and 2 weekdays which will be reviewed by the RD for adequacy every two weeks. This diary will
6 be included in the patient booklet provided. Patients will also be asked to self-monitor weight.
7 Participants will then receive feedback based on their progress. If a patient fails to meet expected
8 outcomes, the patient will be asked to return for a follow-up visit and re-assessment of their
9 nutrition status and nutrition care plan.
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16 17 18 *Psychological support program*

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

37 Exercise will be interrupted if certain specific criteria are met as per CPET international standards:
38 angina, symptomatic arrhythmia, fall in systolic BP >20mmHg, systolic BP >250mmHg or diastolic
39 BP >120mmHg, oxygen saturation <80% on room air, loss of coordination, mental confusion,
40 dizziness or faintness (14). Healthcare workers involved hold advanced cardiac life support
41 certification and access to hospital support. AEs will be assessed by study physician. Incident AEs
42 will be reviewed by the POP team before initiation of exercise. If participant misses a session,
43 they will be contacted to exclude AE. Any serious AE will be reported to the principal investigator
44 within 24 hours and the participant's involvement in the trial suspended until re-assessed.
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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, mid-way through the maintenance phase, and at the end of the maintenance phase (Table 1). The prehabilitation program will end after 24 weeks of study visits, if the participant undergoes liver transplantation, 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 exam, review of laboratory values and assessment of AE will be performed. Study-related data will also be collected as per the description below. Study visits are summarized 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 standardized 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

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3 group over a 5-year period of time reports an adherence of 70 to 98 % with the protocol and a
4 LTFU of 14%(24).
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9 *Secondary objective: Safety*

10 To evaluate the safety of our intervention, we will record all AEs from recruitment until
11 withdrawal from study, or date of surgery to limit selective outcome reporting bias. We will
12 follow the Common Terminology Criteria for AEs v5.0 for grading and reporting AEs(25). AEs will
13 be categorized as related to the intervention or not as assessed by a study physician. Serious AEs
14 will be defined as any AE that leads to hospitalization or death. We will also identify AEs
15 associated with temporary or permanent interruption of the intervention. Our intervention will
16 be considered safe if there are 5% or less serious AEs related to our intervention.
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25 *Exploratory objectives: Effectiveness of the intervention*

26 We will capture a broad range of metrics influenced by our intervention based on previous
27 studies(12). As this is a novel intervention in patients with cirrhosis, the magnitude of change
28 between baseline and follow-up necessary to derive a definite clinical benefit is unclear. For this
29 reason, a positive effect will be defined as any improvement in baseline values compared to the
30 last pre-liver transplant values as assessed by statistical means. For frailty, we will monitor for
31 change in LFI and proportion of frail individuals. A 0.1 change in LFI is clinically significant(7). For
32 exercise capacity, 6MWT, METS, peak workload, peak VO₂ will be assessed. A 14 to 30m change
33 in 6MWT, a 6% increase in peak VO₂ or a 1.0mL/kg/min change in peak VO₂ are considered
34 clinically significant, but this is not validated in cirrhosis(26, 27). For muscle mass and strength,
35 we will assess change in HGS. Malnutrition will be assessed by a change in RFH-GA class or a
36 change in proportion of severely malnourished individuals. Interval improvement in CLDQ will
37 confirm the positive impact of our program on HRQoL. We will assess delisting due to death or
38 being too unwell.
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52 We will capture postoperative outcomes that might improve following prehabilitation. The type,
53 frequency, and severity of complications will be recorded and summarized using the CCI(28). We
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3 will also record hospital LOS in days, non-home discharge (home vs not home), re-admission and
4 mortality at 3- and 12-months.
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8 9 **Data collection**

10 We will record baseline age, sex, gender, smoking status, alcohol consumption status, history of
11 diabetes, aetiology of liver disease, albumin, bilirubin, INR, ascites, HE, creatinine, sodium,
12 presence of HCC, history and type of decompensated liver disease (varices, ascites, HE), history
13 of cardiovascular disease, and history of dyslipidaemia at initial visit. Reason for refusal to
14 participate in the study will be collected by the treating hepatologist and transmitted to the
15 research team to avoid contacting participants who have refused to participate. Research
16 personnel will record reason for lack of protocol adherence and LTFU. At baseline, and at pre-
17 specified visits during the intervention, LFI, peak VO₂, peak workload, METS, 6MWT, HGS, RFH-
18 GA, BMI, and CLDQ will be recorded by the research personnel. Participant diary will be reviewed
19 with the kinesiologist and dietician and respective data entered accordingly. AEs will be recorded
20 as per above. HGS will be measured using a handheld dynamometer. Research personnel will
21 follow patients throughout their time in the prehabilitation program and during their hospital
22 course recording all data and outcomes as set out in the aims above. Research personnel will
23 review participant data at each study visit for new events. Mortality at 3- and 12-months will be
24 assessed through chart review, and contacting participant if necessary. If an outcome has
25 occurred, the study team will obtain the appropriate documentation. All patient data will be
26 coded. Study personnel will submit the trial data by completing the Case Report Forms through
27 a secure web-based password protected data collection program (RedCAP). Source
28 documentation supporting the trial will be made available for trial related monitoring, audits,
29 and institutional ethics review.
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49 **Statistical analysis**

50 To address the feasibility objective, we will report recruitment, adherence, LTFU, study
51 withdrawal as frequencies (percentages). Reasons for the following will be recorded: refusal to
52 participate in eligible patients, lack of adherence, LTFU, and study withdrawal. Reasons will be
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3 categorized and reported as proportion (percentages). To address the safety objective, we will
4 report AEs as event frequency per-type, and per-patient. We will separately report and describe
5 serious AEs related to the intervention. To assess the impact of our intervention, we will perform
6 this analysis in all recruited patients. We will also perform a separate analysis for those that
7 adhered and those that did not adhere to protocol. We will report LFI, 6MWT, peak VO₂, peak
8 workload, METS, HGS, RFH-GA, CLDQ as continuous variables using means (SD) or medians (IQR).
9 We will report the frequency (percentage [%]) of frail patients and severely malnourished
10 patients. The variables will be presented at baseline and at pre-specified visits before liver
11 transplantation. Paired data (before/after) will be compared using Wilcoxon Signed Rank Test
12 analysis for continuous variables without normal distribution, t-test for continuous variables with
13 normal distribution, and Fisher's exact for categorical variables. To account for the variability in
14 follow-up, the protocol was developed in a way to have multiple assessment time points
15 throughout the study. Patients will be assessed based on the number of assessment visit
16 completed. The frequency (%) of patients delisted due to death or being too unwell will be
17 reported. To assess the impact of our intervention on postoperative outcomes, we will perform
18 this analysis on the sub-group of patients that underwent liver transplantation. We will also
19 separately assess postoperative outcomes in patients that have adhered and those that have not
20 adhered to our protocol. We will report the type, frequency, and severity of complications, CCI,
21 LOS, and re-admissions at 3-months as continuous variables using means (SD) and medians (IQR).
22 Non-home discharge and death at 3- and 12-months will be reported as frequency (%). Where
23 applicable, 95% CI will be reported. All p-values are two-tailed, and values <0.05 will be
24 considered statistically significant. Analyses will be performed using SPSS (v24.0). Reporting will
25 be in accordance with the CONSORT guidance for non-randomized feasibility studies(22, 29).
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47 **Sample size and timeline**

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49 Due to the feasibility nature of the proposed trial, we propose a convenient sample size of 25
50 participants using currently available literature(15, 23, 30). As this is a feasibility study with
51 potential unforeseen obstacles, we expect 30 months to finalize recruitment and completion of
52 the study visits.
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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. Adverse events 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 (example: 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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AUTHORS' CONTRIBUTIONS

All authors listed have significantly contributed to the conceptualization and design of this study directed by Dr. Amine Benmassaoud, Dr. Franco Carli and Dr. Amal Bessissow. In addition, Dr. Chelsia Gillis contributed her expertise to the nutritional intervention, Rashami Awasthi to the exercise program, Linda Edgar to the psychological support program, Myriam Martel to the statistical analysis, Olivia Geraci to data collection and interpretation, and Dr. Jeffrey Barkun, Dr. Tianyan Chen, and Dr. Giada Sebastiani to the pre-and post-transplant considerations.

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COMPETING INTEREST STATEMENT

All others have no competing interests to declare for this study.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request.

Table 1. Organization 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
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)					