PREHABILITATION IN PATIENTS WITH CIRRHOSIS AWAITING LIVER TRANSPLANTATION

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ENGLISH ABSTRACT

Background

Patients with cirrhosis awaiting liver transplantation are often frail, malnourished, and sarcopenic. These conditions increase their risk of worse outcomes before and after liver transplantation. Prehabilitation attempts to optimize a patient's overall fitness before a major surgery through exercise training and nutritional optimization. To date, it is unclear whether prehabilitation in patients with cirrhosis awaiting liver transplantation is beneficial. The objectives of this thesis are to assess the feasibility and safety of a prehabilitation program in patients with cirrhosis awaiting liver transplantation.

Methods

This is an unblinded single arm feasibility study recruiting adult patients with cirrhosis that are active on the liver transplant waiting list at the McGill University Health Centre. Patients will be excluded based on criteria established for the safe exercise training of patients with cirrhosis. Individuals recruited will participate in a multimodal prehabilitation program combining exercise training, nutritional optimization and psychological support. The primary feasibility objective of this study is to evaluate study recruitment and protocol adherence. The secondary objective is to assess safety of the intervention by recording the incidence of serious and non-serious adverse events (AE). Exploratory objectives will assess interval change in markers of frailty, muscle mass, nutritional status and health related quality of life. This feasibility study aims to recruit 20 participants. As this is an ongoing clinical trial, data collected from December 6th, 2021 to October 28th, 2022 is presented (NCT05237583, MUHC Study ID 2021-7646).

Results

Of the 54 participants that met inclusion criteria, 15 (27.8%) had an exclusion criteria. Most common cause for exclusion was a Model for end stage liver disease score > 20 (33.3%). Thus far, of the 39 eligible patients, 14 were approached. Ten (71.4%) eligible participants refused to enroll in the study while 4 (28.6%) were recruited. Most common cause reported for refusal to participate was visit requirements in 5 (50%). Of the 4 recruited participants, adherence to study exercise visits during the induction phase was 91.7%, while it was 80.0% during the maintenance phase. Of the 38 exercise visits, there was one non-serious AE (abdominal pain) possibly related to the intervention which led to discontinuation of the study. Compared to baseline, all exercise capacity markers increased, but this was not statistically significant. Health related quality of life increased by the end of induction, but decreased during maintenance phase.

Conclusions

Based on our preliminary data, although recruitment is lower than expected, the intervention appears to be safe as there have been no serious AEs. Exercise metrics may be positively impacted by the prehabilitation program, but this observation is based on a low number of participants and an incomplete study. This study will continue to recruit participants until we reach the target sample size and report our complete findings.

ABBRÉGÉ EN FRANÇAIS

Contexte

Les patients atteints de cirrhose et en attente d'une greffe hépatique sont fragiles, dénutris, et sarcopéniques. Ces conditions augmentent leur risque de complications avant et après une greffe. La préadaptation a pour but d'optimiser la condition physique avant une intervention chirurgicale majeure par le biais d'un entraînement physique. À ce jour, il est incertain si la préadaptation chez les patients atteints de cirrhose en attente d'une greffe hépatique est bénéfique. Les objectifs de cette étude sont d'évaluer la faisabilité, et la sécurité de la préadaptation chez les patients atteints de cirrhose en attente d'une greffe hépatique.

Méthodes

Il s'agit d'une étude de faisabilité sans insu à un seul bras recrutant des patients adultes atteints de cirrhose qui sont actifs sur la liste d'attente de greffe hépatique au Centre Universitaire de Santé McGill. Les patients seront exclus en fonction de critères établis pour un entraînement physique sécuritaire chez les patients atteints de cirrhose. Les personnes recrutées participeront à un programme de préadaptation multimodal combinant un entraînement physique, et une optimisation nutritionnelle. Le principal objectif de faisabilité de cette étude est d'évaluer le recrutement et l'adhésion au protocole. L'objectif secondaire est d'évaluer la sécurité de l'intervention en enregistrant l'incidence des événements indésirables graves et non graves. Des objectifs exploratoires permettront d'évaluer les changements dans les marqueurs de fragilité, la masse musculaire, l'état nutritionnel et la qualité de vie reliée à la santé. Cette étude de faisabilité vise à recruter 20 participants. Comme il s'agit d'un essai clinique en cours, les données

recueillies du 6 décembre 2021 au 28 octobre 2022 sont présentées (NCT05237583, MUHC Study ID 2021-7646).

Résultats

Sur les 54 participants répondant aux critères d'inclusion, 15 (27,8 %) avaient un critère d'exclusion. La cause la plus fréquente d'exclusion était un score du modèle de maladie hépatique au stade terminal > 20 (33,3 %). Sur les 39 patients éligibles, 14 ont été approchés. 10 (71,4 %) participants admissibles ont refusé de participer à l'étude, tandis que 4 (28,6 %) ont été recrutés. La cause la plus fréquente du refus de participer était reliée à la fréquence des visites dans 5 cas (50 %). Parmi les 4 participants recrutés, l'adhésion aux visites d'exercice pendant la phase d'induction était de 91,7 %, et de 80,0 % pendant la phase de maintien. Sur les 38 visites d'exercise, il y a eu un événement indésirable non grave probablement lié à l'intervention qui a conduit à la discontinuation de l'étude. Par rapport au début de l'étude, les marqueurs de la capacité d'exercice ont augmenté, mais ce n'était pas statistiquement significatif. La qualité de vie liée à la santé a augmenté à la fin de l'induction, mais a diminué pendant la phase de maintien.

Conclusions

Jusqu'à présent, le recrutement est plus faible que prévu. Toutefois, l'intervention semble sécuritaire puisqu'il n'y a pas eu d'événements indésirables graves. La capacité physique s'est améliorée, mais cette observation est basée sur un faible nombre de participants et l'étude est toujours en cours. Cette étude continuera de recruter des participants et nous communiquerons nos résultats une fois l'étude terminée.

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CONTRIBUTION OF AUTHORS

I, Amine Benmassaoud, am the primary author of this thesis and all of its chapters. Specifically, I drafted each chapter, including all tables and figures included herein. My supervisors, Dr. Amal Bessissow and Dr. Giada Sebastiani, provided critical revision of the entire work presented. Below, I am also describing the contributions of all co-authors involved in this work.

Introduction

Amine Benmassaoud: Conception, design, and drafting. Amal Bessissow: Conception, design, and critical revision. Giada Sebastiani: critical revision.

Chapter 1

Amine Benmassaoud: Conception and design; acquisition, analysis and interpretation of the data; drafting of the chapter. Amal Bessissow: Conception, design and critical revision. Giada Sebastiani: critical revision. Franco Carli: critical revision. Stella Daskalopoulou: critical revision.

Chapter 2

Amine Benmassaoud: Conception and design; analysis and interpretation of the data; drafting of the chapter. Amal Bessissow: Conception, design and critical revision. Giada Sebastiani: Conception, design, and critical revision. Dorsa Alavifard: data acquisition. Rashami Awasthi: conception, design, data acquisition critical revision. Jeffrey Barkun: critical revision. Franco Carli: conception, design, and critical revision. Tianyan Chen: critical revision. Stella Daskalopoulou:

critical revision. Linda Edgar: data acquisition, critical revision. Olivia Geraci: data acquisition. Chelisa Gillis: Conception, design, and critical revision. Ciaran Keane: data acquisition.

Chapter 3

Amine Benmassaoud: conception, design, and drafting of the chapter. Amal Bessissow: critical revision. Giada Sebastiani: critical revision.

Chapter 4

Amine Benmassaoud: conception, design, and drafting of the chapter. Amal Bessissow: critical revision. Giada Sebastiani: critical revision.

Appendix 1

Amine Benmassaoud: Conception, design and drafting. Amal Bessissow: Conception, design and critical revision. Giada Sebastiani: Critical revision. Rashami Awasthi: Conception, design, and drafting. Jeffrey Barkun: Critical revision. Franco Carli: Conception, design, and drafting. Tianyan Chen: Critical revision. Chelisa Gillis: Conception, design, and drafting.

Appendix 2

Amine Benmassaoud: Conception, design and drafting. Amal Bessissow: Critical revision. Giada Sebastiani: Critical revision. Dorsa Alavifard: Critical revision. Rashami Awasthi: Critical revision. Franco Carli: Critical revision. Chelisa Gillis: Critical revision.

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LIST OF ABBREVIATIONS

6MWT	6 minute walk test
95% CI	95% Confidence interval
AE	Adverse event
AT	Anaerobic threshold
BP	Blood pressure
BMI	Body mass index
CDTRP	Canadian Donation and Transplantation Research Program
CPET	Cardiopulmonary exercise testing
CP	Child Pugh score
CLDQ	Chronic liver disease questionnaire
EQ5D-5L	EuroQoL 5Dimension 5-Level
HGS	Handgrip strength
HRQoL	Health-related quality of life
HE	Hepatic encephalopathy
HCC	Hepatocellular carcinoma
HIIT	High intensity interval training
HBEP	Home-based exercise program
HADS	Hospital anxiety and depression score
ICF	Informed consent form
ICU	Intensive care unit
INR	International normalized ratio
IQR	Interquartile range

LOS	Length of stay
LFI	Liver frailty index
LTFU	Loss to follow-up
MUHC	McGill University Health Centre
MAMC	Mid upper-arm muscle circumference
MELD	Model for end-stage liver disease
NAFLD	Non-alcoholic fatty liver disease
peakVO2	Oxygen consumption at peak exercise
POP	Preopoerative program
RCT	Randomized controlled trial
RR	Risk ratio
RD	Registered dietician
REE	Resting energy expenditure
RFH-GA	Royal Free Hospital Global Assessment
RFH-NPT	RFH-nursing prioritization tool
SF-36	Short form 36 questionnaire
SPPB	Short physical performance batter
SD	Standard deviation
TIPSS	Transjugular portosystemic shunt insertion
L3-PMI	Total psoas muscle index at 3rd lumbar vertebrae
L3-SMI	Total cross-sectional skeletal muscle index at 3rd lumbar vertebrae
W	Watts

INTRODUCTION

Cirrhosis represents the end-stage of advanced liver disease. It develops after years of repeated hepatic injury and formation of hepatic nodules with dense fibrous septa[1]. It is the 14th most common cause of death worldwide with an estimated 1.03 million deaths per year[2]. Unfortunately, recent years have shown a 47% increase in mortality cases of cirrhosis[3].The most common causes of cirrhosis worldwide include infection with the Hepatitis B or Hepatitis C virus, alcohol-related liver disease, and non-alcoholic fatty liver disease (NAFLD). Other causes include autoimmune and cholestatic liver diseases, such as autoimmune hepatitis, primary sclerosing cholangitis, and primary biliary cholangitis, or genetic diseases, such as hereditary hemochromatosis, alpha-1-antitrypsin deficiency, and Wilson's disease. Current trends suggest that NAFLD is the most rapidly growing contributor to liver mortality[4].

In its early stages, cirrhosis is a silent disease, meaning that it causes no symptoms. Most patients are asymptomatic until an episode of hepatic decompensation occurs, which includes the presence of clinically significant ascites, variceal bleeding, or hepatic encephalopathy (HE)[5]. Patients can also present with an episode of jaundice or a hepatobiliary malignancy such as a hepatocellular carcinoma (HCC) or a cholangiocarcinoma. The development of decompensated cirrhosis is an important milestone as the median survival of patients with compensated cirrhosis is 12 years whereas it is only 2 years in those that have decompensated[5]. The progression from compensated to decompensated cirrhosis is driven by worsening portal hypertension, a hemodynamic syndrome. Portal hypertension occurs due to increased intrahepatic vascular

resistance and portal venous flow[6]. In the early stages of cirrhosis, portal hypertension is primarily caused by increased vascular resistance from fibrotic nodules obstructing the flow of blood through the hepatic sinusoids. In later stages, there is a relative increase in vasodilators, such as nitrous oxide, at the level of the splanchnic arterioles leading to an increase in portal venous inflow. As resistance and flow increase within the portal venous system, portal pressure increases to reach dangerously high levels and promotes hepatic decompensation.

Liver transplantation

In patients with decompensated cirrhosis where death is inevitable, liver transplantation becomes a life-saving procedure. Based on a multicenter retrospective review of liver transplantation outcomes in Canada, recipients of a deceased liver transplant have a survival of 91.1% at 1 year, 85.5% at 3 years, 83.9% at 5 years, and 72.4% at 10 years[7]. This is in stark contrast with the expected median survival of 2 years seen in patients with decompensated cirrhosis[5]. Due to organ shortage, the liver transplant waiting list is organized based on medical urgency as reflected by the Model for End-stage Liver Disease (MELD) score[8]. This score incorporates serum bilirubin, creatinine, and international normalized ratio (INR), and ranges between 6 and 40. Unfortunately, the MELD score does not adequately capture the survival of individuals with HCC, or hyponatremia, predictors of increased mortality[9]. For this reason, individuals with HCC are granted exception points above their biological MELD score, while those with hyponatremia are given more points through the MELD-Na score which has been accepted by the Organ Procurement and Transplantation Network in 2016[10]. Despite attempts to improve organ prioritization and allocation, a study from Alberta where the mean time to transplantation was

450 days showed that about 10% of individuals die while waiting for liver transplantation[11]. Another 10% of individuals with cirrhosis are removed from the waiting list as they become too unwell to receive a liver transplantation[11].

Frailty in patients with cirrhosis

Frailty, which is defined as a state of physiologic vulnerability predisposing an individual to adverse health outcome, has been increasingly recognized in patients with cirrhosis as a major predictor of mortality independently of the MELD score. Indeed, for the same MELD score, frail patients with cirrhosis do worse than if they were robust[12]. Furthermore, combining frailty with the MELD-Na score improves the prediction of 3-month mortality with an area-under the curve of 0.79 for the combined score versus 0.73 for MELD-Na alone. The prevalence of frailty in patients with cirrhosis varies between 15-40% depending on the population studied and the frailty score used [12-14]. Common tools used to assess frailty include the Clinical Frailty Scale, Fried Frailty Phenotype, the Liver Frailty Index (LFI), the 6 minute walk test (6MWT), the short physical performance battery (SPPB), the 4m gait speed, or the handgrip strength (HGS) alone[15]. These tools and their components are summarized in Table1. Experts have suggested that if one test can be done, they suggest the 4m gait speed with either the SPPB or the LFI[16]. The LFI takes 3 to 5 minutes to do and is highly reproducible (instructions summarized in Appendix 2). The intraclass correlation coefficient of the LFI is 0.93 (95% confidence interval of 0.91-0.95) confirming an excellent interobserver agreement[17]. Individuals are then classified based on a numerical score as either robust (below 20th percentile), pre-frail (between 20th-80th percentiles), or frail (above 80th percentile). The percentile represents the distribution of LFI in more than 1,400 outpatients

with cirrhosis awaiting liver transplantation. Studies have shown that the LFI predicts mortality on the liver transplant waiting list, and that worsening LFI is associated with a further increase in mortality risk[18]. Following liver transplantation, LFI predicts longer hospital and intensive care unit (ICU) length of stay, higher healthcare utilization, non-home discharge, and mortality[19]. Of the frailty metrics described, the LFI is the most commonly used. Assessment of frailty is therefore an important component of the stratification of patients awaiting liver transplantation. Unfortunately, at this time, frailty is not used to prioritize individuals on the waiting list and can explain why some become too ill while waiting. This is in part due to the fact that it is unclear how to best include frailty in the prioritization scheme for liver transplantation.

Table 1. Summary of available tools capable to identify frailty in people with cirrhosis.

Frailty assessment tool	Components
4m gait speed	Time taken to walk 4 meters
6 minute walk test	Distance walked during a 6 minutes time
Clinical Frailty Scale	Pictogram depiction of activities an individual is capable of maintaining
Fried Frailty Phenotype	Weight loss, handgrip strength, exhaustion, time to walk 15 feet, low physical activity
Handgrip strength	Force used to grip a handheld dynamometer
Liver Frailty Index	Sex-specific score combining dominant handgrip strength, time to do 5 chair stands, and time holding a 3 position balance
Short Physical Performance Battery	4m gait speed, time to do 5 chair stands, and time holding a 3 position balance

Malnutrition in patients with cirrhosis

In addition to frailty, patients with cirrhosis suffer from poor nutrition. It is estimated that about 5-99% of patients are not adequately nourished[20]. Despite a high prevalence of malnutrition and knowledge of its nefarious impact on patients with cirrhosis, it is often not included in the standard assessment of patients due to its subjectivity. More recently, an objective tool has been developed and specifically validated in people with cirrhosis. This tool, called the Royal Free Hospital Global Assessment (RFH-GA), categorizes patients into three groups, namely adequately

nourished, moderately malnourished and severely malnourished[21]. It incorporates 3 objectively obtained variables, including the body mass index (BMI), the mid upper-arm muscle circumference (MAMC), and dietary intake. Severe malnutrition by RFH-GA is associated with increased pre-transplant mortality, and post-transplant infections, prolonged mechanical ventilation, and prolonged hospital and ICU stay[21, 22]. One of its drawbacks is that it requires a trained dietician. Despite that, it was shown to have high interobserver agreement (kappa = 0.79) [21]. Another drawback is that a dry weight has to be extrapolated by subtracting the predicted weight of ascites and body edema. This limitation is commonly seen for the weight assessment of patients with cirrhosis. Another tool called the RFH-nursing prioritization tool (RFH-NPT) can be used to identify those that would benefit from a nutritional intervention[20]. As opposed to the RFH-GA, the score varies from 0 to 7. Those with a score of 0 are considered well nourished and unlikely to benefit from a nutritional intervention while those with a score of 1 are at intermediate risk, and those above 2 are at high risk and should be referred to a dietician. This tool is often used as an initial screening method, while its ability to respond to an intervention is not clear (instructions summarized in Appendix 2).

Table 2. Components of the Royal Free Hospital – Global Assessment

Components	**Approach**
Dry body mass index	Divided into < or ≥ 20kg/m^2
Mid upper-arm muscle circumference	Divided into < or ≥ 5th percentile based on age and sex
Dietary intake	Divided into adequate, inadequate or negligible based on calorie counting
Subjective override	Able to move up or down 1 category based on the clinical judgment of the trained dietician

Sarcopenia in patients with cirrhosis

A third major determinant of prognosis in patients with cirrhosis is the presence of sarcopenia or low muscle mass. Its prevalence is also very high in patients with cirrhosis, varying between 20-50%[23]. Cross-sectional imaging with secondary image analysis can be used to determine muscle mass. The most frequently used parameters are the total psoas muscle area or the total cross-sectional skeletal muscle area, both measured at the 3rd lumbar vertebrae and indexed by the height squared, namely L3-PMI and L3-SMI[16]. A recent consensus statement defined sarcopenia in patients with cirrhosis as a L3-SMI < 50cm^2/m^2 for males and < 39cm^2/m^2 in females[24]. Its presence is associated with significantly worse survival on the liver transplant waiting list[25, 26]. The median survival of a person with sarcopenia was 19 months compared to 34 months for someone without sarcopenia on the liver transplant waiting list[25]. Sarcopenia is also an independent predictor of increased post-transplant mortality, longer hospital and ICU stay, as well as higher incidence of infections[22]. Other surrogates to estimate muscle mass include the

HGS and the MAMC. The HGS can be easily applied in the clinical setting, while the MAMC requires further training. At this moment, none of these tools are routinely obtained for clinical purposes.

Optimization of patients with cirrhosis

The mechanisms that predispose individuals with cirrhosis to malnutrition, sarcopenia and ultimately frailty are diverse and often incompletely understood. These mechanisms interact at multiple levels and together lead to the development of frailty. From a nutritional point of view, impaired dietary intake is common in patients with cirrhosis[27]. The presence of gastrointestinal symptoms such as nausea, vomiting, early satiety and dysgeusia contribute to decreased oral intake. This can be further worsened by the presence of ascites, and splenomegaly. Beyond a deficient intake, malabsorption is driven by portal hypertensive enteropathy and a decreased production of bile acids, which impairs the absorption of fat and other nutrients[20]. Furthermore, impaired metabolism of carbohydrates and a low glycogen store lead to a catabolic state where muscles are broken down for energy purposes. Other contributors to sarcopenia and muscle loss includes ammonia, decreased testosterone and growth hormone, and endotoxemia[28].

To address malnutrition, sarcopenia, and frailty in patients with cirrhosis, exercise training with nutritional optimization is recommended[16]. Exercise is believed to improve muscle mass and quality, decrease vascular stiffness, improve mitochondrial activity, increase bone mineral density, and lower hepatic steatosis and portal hypertension through pleiotropic mechanisms that are not fully understood[16]. It can also lead to lower body fat, improve insulin sensitivity,

cognitive function and quality of life[16]. A recent systematic review published in 2019 summarized the available literature related to the impact of physical exercise on the physical frailty of patients with cirrhosis[29]. They identified 4 studies in patients with decompensated cirrhosis (sample size ranges from 8 to 33), and 7 in patients with compensated cirrhosis (sample size 1 to 60). This review, which is not limited to patients on the transplant list, reported that exercise was associated with an improvement of exercise capacity, of muscle mass, and a reduction in fatigue. It also reported a highly variable adherence to exercise programs. Though not formally assessed, they commented that a home-based exercise program (HBEP) combining walking and resistance training was feasible and safe and that a 12 week duration was the minimum to improve physical frailty[29]. Another review from 2017 identified 4 randomized controlled trials (RCT) with total sample size of 81 patients in people with cirrhosis[30]. They noted that there were no severe adverse events (AE), and that liver disease was not worsened by exercise. They could not identify changes in 6MWT and oxygen consumption at peak exercise. While it is suspected to be beneficial, not all patients with cirrhosis can exercise. To ensure the safety of such an intervention, it is crucial to screen patients for contra-indications related to cirrhosis, cardiovascular diseases, or other comorbidities as recommended by an expert panel from six North American centres[16].

For this reason, prehabilitation, which aims to optimize the pre-operative physical condition of surgical candidates, has generated a lot of interest in patients awaiting liver transplantation. Prehabilitation combines a backbone of exercise training with or without nutritional optimization. In 2019, the Canadian Donation and Transplantation Research Program (CDTRP)

and the Canadian Network for Rehabilitation and Exercise for Solid Organ Transplant Optimal Recovery released a consensus report stating that prehabilitation is understudied, especially in liver transplant candidates, and that future research should focus on the feasibility, acceptability and effectiveness of these programs[31]. In addition, effects of prehabilitation on waitlist outcomes, such as healthcare utilization, mortality, frailty, and early post-transplant clinical outcomes, such as hospital length of stay (LOS) should be further investigated[31]. The consensus conference on frailty sponsored by the American Society of Transplantation has highlighted similar research areas as a priority to improve outcomes following liver transplantation[32].

To investigate the impact of prehabilitation on this patient population, we present in Chapter 1 a comprehensive literature review structured as a scoping review to assess the feasibility, safety, and effectiveness of prehabilitation in patients with cirrhosis on the liver transplant waiting list. Incorporating the knowledge gaps identified in the comprehensive literature review, in the body of the thesis, we present the protocol and preliminary results of a feasibility study evaluating the feasibility, safety, and effectiveness of prehabilitation in patients with cirrhosis awaiting liver transplantation in Chapter 2. We hypothesize that patients with cirrhosis awaiting liver transplantation can safely participate in exercise training if we incorporate the recently published screening criteria. We expect that prehabilitation will lead to an improvement in their exercise capacity and that this would translate into better pre- and post- transplantation outcomes. We then discuss all of the findings in Chapter 3. In fine, we present our conclusions and future directions in Chapter 4.

CHAPTER 1

COMPREHENSIVE LITERATURE REVIEW: PREHABILITATION IN PATIENTS WITH CIRRHOSIS AWAITING LIVER TRANSPLANTATION, A SCOPING REVIEW

1.1 INTRODUCTION

Liver transplantation is a major life-saving abdominal surgery for patients with decompensated liver disease whose expected survival is only of a few months[5]. Ranking on the waitlist is determined by the MELD score, which prioritizes patients based on medical urgency[8]. Despite this, 10-20% of individuals on the liver transplant waiting list become too sick or die before receiving an organ[11]. Although this can be partly explained by organ shortage, the presence of frailty, sarcopenia, and malnutrition, which are unaccounted for in the MELD score, further contributes to patients falling off the waitlist[19, 22, 25]. Recent evidence suggests that for the same MELD score, a frail individual will have a worse survival than one who is robust[12].

Patients with cirrhosis active on the liver transplant list wait a few weeks to months before receiving an organ. This time window provides a unique opportunity for interventions targeting frailty, sarcopenia, and malnutrition. Prehabilitation programs are implemented between the decision to operate and the surgery itself to improve the physical fitness of patients[33]. These programs often include a backbone of exercise training with or without nutritional optimization.

As highlighted in a recent meta-analysis, these interventions have shown some benefit in patients awaiting a major surgical procedure, but the quality of the evidence is considered low[34]. In addition, the interventions are highly heterogeneous which limits meaningful comparisons. In the current context, the American and Canadian transplantation societies have encouraged further studies on prehabilitation in patients awaiting organ transplantation[31, 32].

The objectives of this scoping review are to determine whether prehabilitation in patients with cirrhosis awaiting liver transplantation is feasible, and safe, and whether it leads to a change in clinical parameters before or after transplantation. Although preliminary evidence suggests that exercise training is safe in patients with cirrhosis, it is unclear if this is the case in patients active on the liver transplant waiting list[29, 30]. In order to evaluate the available literature, we performed a scoping review to inform the foundation of a future clinical trial. We chose to perform a scoping review instead of a meta-analysis as the current body of evidence is mostly constituted of studies with very heterogeneous inclusion criteria and outcome measures.

1.2 METHODS

We aimed to characterize the available knowledge on the impact of prehabilitation in patients with cirrhosis awaiting liver transplantation. We focused on the feasibility, safety, and effectiveness of such an intervention in this population. A formal protocol was developed using the PRISMA checklist for scoping reviews[35].

1.2.1 Search strategy

Following discussion with a medical librarian, I searched the following databases: PUBMED, EMBASE, EMBASE Classic, OVID Healthstar, and OVID MEDLINE, from Inception to February 2022. The following systematic search strategy was employed to retrieve potential studies: ((prehabilitation) OR (((exercis*) OR (physic*)) AND ((train*) OR (interven*) OR (prescrip*)))) AND ((liver transplant*) OR (cirrhos*) OR (advanced liver diseas*)) AND Adult. All results were compiled using EndNote X9.

1.2.2 Study selection

To answer the aims of our scoping review, we selected studies if they included: i) potential candidates or actively listed individuals for liver transplantation; ii) an exercise training program with or without a comparator arm; iii) endpoints including feasibility, and/or safety, and/or effectiveness on pre- and post-transplant outcomes. We excluded studies of children (<18 years old), non-English publications, conference abstracts, non-prospective studies and case reports. Studies that evaluated exercise training following liver transplantation were excluded as not relevant to our aims. All titles and abstracts were reviewed by Amine Benmassaoud for relevance. Potentially eligible studies were then retrieved and the full-text was reviewed to decide on inclusion or exclusion based on the described eligibility criteria.

1.2.3 Data extraction and analysis

Studies included in the final review were thoroughly analyzed and key information was retrieved. Specifically, we extracted information related to study design, sample size, description of the

included participants, description of the prehabilitation intervention, and all endpoints related to feasibility, safety, and effectiveness of the intervention.

To assess feasibility, I recorded: i) the number of participants who were approached, enrolled, and completed the study; ii) the number of sessions attended; and iii) reasons for refusal to participate, loss to follow-up, or lack of adherence.

To assess safety, I retrieved: i) the number of AEs; ii) the type and severity of the AE; iii) whether it was related to the intervention; and iv) whether it led to study discontinuation. We noted if a protocol was in place to systematically identify AEs.

To assess the effectiveness of the intervention on pre-liver transplantation outcomes, I noted: i) the magnitude and direction of changes in exercise capacity, nutritional status, and HRQoL; and ii) the number of patients that died or were removed from the liver transplant waitlist because of being too unwell. For post-transplantation outcomes, we recorded: i) the number of individuals who were transplanted; ii) their length of hospital or intensive care unit stay; iii) the number and severity of post-operative complications; iv) the discharge destination; and v) mortality.

Data was entered in a pre-formatted Microsoft Excel sheet. Investigators of the included studies were not contacted to confirm the reported data or obtain missing information. Formal critical

appraisal of individual sources of evidence was not performed. We followed the PRISMA checklist for the reporting of scoping reviews[35].

1.3 RESULTS

1.3.1 Overview

The initial search strategy retrieved 2265 citations and after review of title and abstract, 88 articles were considered of potential interest. After further review of the study abstract or full-text if needed, 4 studies met all eligibility criteria and were included in the present review (Figure 1). A summary of the findings presented in this scoping review is included in Table 3.

Figure 1. Flow chart of included studies

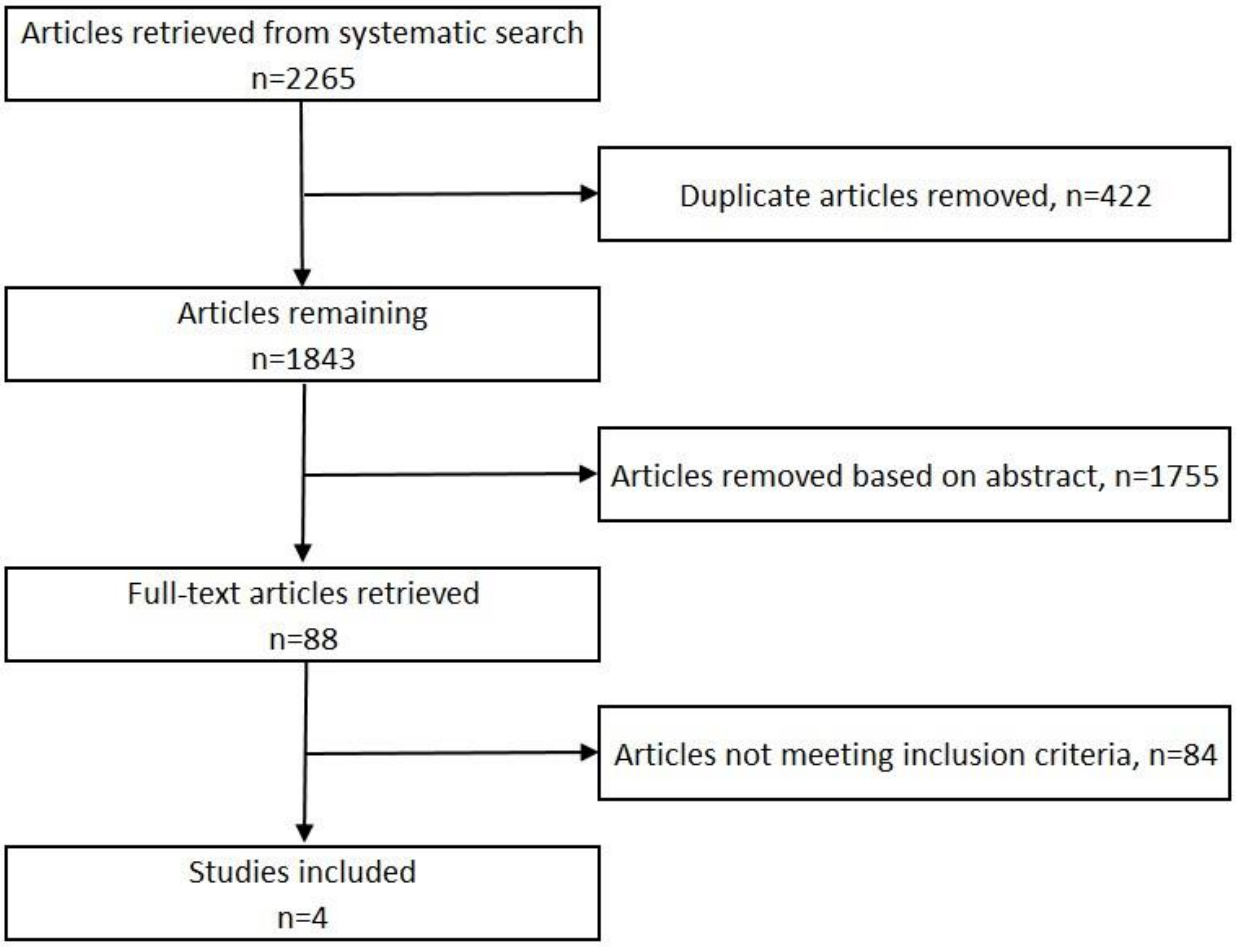


Table 3. Summary of the studies included in the scoping review

Author, year, Country	N	Study design	Inclusion	Exclusion	Intervention	Control	Duration	Aims	Results
Debette, 2015, France	13	Prospective	18-65yo Eligible for LT 1º/2º against EVB Negative EST LVEF > 45%	Any problem prohibiting exercise	At hospital: 2/week, 2hr each Aerobic: cycle ergometer at VT Resistance: weight bench	None	12 weeks	Acceptability Safety Exercise capacity HRQoL	13/13 accepted to participate 8/13 completed 12 weeks 1/13 did not complete due to illness No CV or Cirrhosis deterioration Per-protocol analysis: Peak VO_2: 21.5 to 23.2mL/kg/min, p0.008 6MWD: 481 to 521m, p=0.02 Isometric Quadriceps strength: 30 to 37kg, p0.008 No change in HRQoL
Morkane, 2020, UK	33	Prospective, if live near hospital	>18yo Cirrhosis Awaiting LT	LT for Cancer CI to exercise	At hospital: 3/week, 40min each Aerobic: HIIT on cycle ergometer Nutrition advice N=16pts	SOC + nutrition advice N=17pts	6 weeks	Feasibility Adherence Safety Exercise capacity Post-transplant outcomes	16/29 approached agree to participate 9/16 completed 6 weeks (4=illness, 2=LT, 1=knee pain) Compliance of 94% in the 9 participants No AE related to exercise No worsening of cirrhosis post exercise Peak VO2: 16.2 to 18.5mL/kg/min, p0.02 vs 19 to 17.1mL/kg/min, p0.03 HGS: 26.4 to 29.4kg, p0.05 vs 29.1 to 30.5, p=NS MAMC: no change PostLT LOS (7 vs 9): 13 vs 30days, p=0.02
Wallens, 2019, Australia	21	Randomized controlled trial	18-69yo Candidate for LT	Prior LT Combined T_x Smoking AE at CPET Poor DM	At hospital: 2/week + At home: 1/week Aerobic: stationary bike or walking	SOC N=11pts	8 weeks	Feasibility Adherence Safety Exercise Capacity HRQoL	38 assessed 12 refused due to travel and time issues. No serious AE No cirrhosis complication

				Limitation to exercise	Resistance training N= 10pts			Post-transplant outcomes	AE: 1 relate to knee injury Adherence: 95% to supervised, 75% to unsupervised Time to LT: same PostLT complications: same Death at 90days: same Peak VO2: better by 470mL/min 6MWD: better by 100m HGS: same Thigh pull: same CLDQ: same
Williams, 2019 UK	18	Prospective, CPU random sampling	>18yo Awaiting 1st LT	CV instability Overt HE Inpatient	At home: Aerobic: daily step goals Resistance training: 2/week Additional walk x 10mins x 3/day Nutritional optimization	None	12 weeks	Feasibility Adherence Safety Exercise capacity HRQoL Post-transplant outcomes	46 randomly selected 32/46 were eligible 6/32declined to participate and 8 got LT 18 were enrolled No AE related to program Adherence: DSG: 82%, Exe: 90% at 6wks vs DSG: 53% vs Exe: 78% at 12wks ISWT: +210m, p<0.01 Median DSG: + 2700steps/day SPPB: +2 HADS: same EQ-VAS: + 18% at 12wks, p0.04

Legend: N = number, CI = contra-indication, CPU = central processing unit, CV = cardiovascular, DM = diabetes mellitus, DSG = daily step goals, ISWT = incremental shuttle walk test, LT = liver transplantation, LVEF = left ventricular ejection fraction, SOC = standard of care.

1.3.2 Characteristics of sources of evidence

The studies identified were all self-described as pilot or feasibility studies, were published within the last 10 years and originated from Australia, France, or the United Kingdom. In terms of study design, 3 were prospective (Debette-Gratien et al, 2015; Williams et al, 2019; Morkane et al, 2020), and 1 was a randomized controlled trial (Wallen et al, 2019)[36-39]. The studies by Morkane and Wallen included a comparator arm of usual care while the other studies only had an interventional arm. The number of recruited participants was 13, 18, 21 (10 in the intervention arm and 11 in the control arm), and 33 (16 in the intervention arm and 17 in the control arm) for the studies by Debette, Williams, Wallen and Morkane respectively. Overall, the number of participants available enrolled in an exercise program was 57, and there were 28 individuals in a control group. Only the study by Williams published a protocol ahead of the main publication[40].

1.3.3 Description of participants' selection criteria

All 4 studies included adult participants, but only the study by Debette and Wallen had both a lower and upper age limit of 18 to 65 years, and 18 to 69 years, respectively. The study by Morkane included participants above the age of 18 years without specifying an upper limit. Finally, Williams et al included adult participants without stating a lower or upper age limit. These subtle differences can have an impact on the overall feasibility of an exercise program. In terms of the liver transplant listing status of eligible participants, the studies by Debette, Morkane and Williams included patients on the liver transplant list, while the study by Wallen recruited potential liver transplant candidates. In addition, only the study by Morkane required the diagnosis of cirrhosis as inclusion criteria. The other studies recruited participants without

cirrhosis as long as they needed liver transplant. Furthermore, Williams and Wallen only considered patients awaiting a first liver transplant. This was not described in the other studies.

The rest of the inclusion and exclusion criteria were also very different from one study to the next, but were meant to maximize the feasibility and safety of their intervention. To maximize feasibility, the study by Morkane only recruited participants that lived close to the hospital. To maximize safety, studies considered the severity of liver disease, the presence of cardiac risk factors, or other conditions that could limit physical exercise. In terms of severity of liver disease, the study by Debette required participants to be on appropriate primary or secondary prevention of variceal bleeding, while the study by Williams excluded patients with significant HE (defined as grade 2 or above). In terms of cardiac risk factors, Debette et al required participants to have a negative stress test, and a left ventricular ejection fraction of 45% or above; Williams et al excluded patients with a history or evidence of cardiac instability; and Wallen excluded those with an AE during the initial cardio-pulmonary exercise testing (CPET), active smoking or uncontrolled diabetes. In terms of limitations to exercise, Debette excluded those with a physical or mental handicap or any other somatic problem prohibiting physical exercise. Wallen excluded those with any orthopedic or neurological limitations to exercise. The study by Morkane was the only study to refer to a specific guidance to assess the eligibility of participants, and excluded those with a contra-indication to exercise training or testing as per the American College of Chest Physicians and the American Thoracic society[41].

1.3.4 Description of the prehabilitation programs and their components

Although all studies offered an exercise program, these varied in setting (supervised vs unsupervised), frequency (number of sessions per week), and duration (number of weeks). Debette and Morkane offered a supervised exercise program with a qualified trainer, Williams conducted a home-based exercise program, and Wallen used a hybrid model. In terms of frequency and duration, the study by Debette conducted 2 supervised sessions per week for 12 weeks (total of 24 sessions), while the study by Morkane offered 3 supervised sessions per week for 6 weeks (total of 18 sessions). The study by Wallen included 2 supervised and 1 unsupervised session per week for 8 weeks (total of 24 sessions). The study by Williams organized a 12-week home-based intervention with twice-weekly exercise session (total of 24 sessions).

1.3.4.1 Exercise component

Once again, the specifics of the exercise program offered were very heterogeneous with no study being similar to another. The studies by Debette and Morkane individualized their exercise program by having participants perform a baseline CPET. The study by Debette measured oxygen consumption at peak exercise (peak VO_2) and the corresponding ventilatory threshold. Each session was then performed on a cycle ergometer where patients would progress through a warm up phase (20% of maximal power, in watts [W]), a progressively incremental phase to reach maximal power at ventilatory threshold, and then a recuperation phase (same as warm-up). The aerobic component would last at least 20 minutes at ventilatory threshold. After the aerobic training, participants performed muscular strengthening exercises for 20 minutes. The study by Morkane only had an aerobic component, without resistance training. The exercise program was

individualized using peak VO_2 and the corresponding anaerobic threshold (AT). Exercises were performed on a cycle ergometer with a warm-up and recuperation phase. Instead of working out at peak power, Morkane delivered a high intensity interval training (HIIT) varying between high and moderate intensity for 30 minutes.

The home based exercise program developed by Williams consisted of a twice-weekly functional resistance training and daily step goals. Resistance training included circuits of squats, lunges, bear crawls and rock press to a rate of perceived exertion score of 12-14 on the Borg Scale with incremental levels of difficulty. Average daily step goals were provided to participants based on their pre-trial daily step count and this was increased on a weekly basis. In addition, participants were advised to do some brisk walking for 10 minutes 3 times per day.

The supervised exercise sessions in the study by Wallen consisted of stationary cycling or walking and a circuit-based resistance training. Unfortunately, they did not provide further description of their program. Participants were then asked to perform the same routine during the unsupervised sessions.

1.3.4.2 Other components

Only two studies offered an intervention beyond exercise training. In the study by Morkane, a trained dietician provided an individualized nutritional assessment and advice at baseline to study participants and again at the end of the intervention at week 6. The assessment was standardized using the RFH-GA questionnaire[21]. In the study by Williams, all patients underwent

nutritional optimization and included a target daily protein intake of 1.2-1.5g/kg/day. This was reviewed every 6 weeks while on the waiting list, and therefore beyond the trial duration itself. The investigators did not elaborate on how the nutritional assessments were conducted. There was no mention of nutritional optimization in the studies by Debette and Wallen, while no study provided psychological support as part of the intervention.

1.3.5 Comparator arms

The studies by Morkane and Wallen included a comparator arm of usual care. In the study by Morkane, participants received nutritional assessment and advice. They were not-randomized to usual care but rather selected to match those participating in the exercise arm based on age, sex, and MELD score. In the study by Wallen, participants were randomized to exercise or usual care group by an individual external to the investigation using a computer-generated allocation program. The same individual generated the randomization code and allocated the participants. This RCT was not blinded. There were no comparator arms in the studies by Debette, or Williams.

1.3.6 Endpoints assessed

The main endpoints for this scoping review included feasibility, safety and effectiveness of prehabilitation in patients awaiting liver transplantation. These were covered by all the included studies.

1.3.6.1 Feasibility

All 4 studies described how many patients were approached, how many participated in the intervention, and how many completed the program. Reasons for refusal to participate and discontinuation of the intervention were also described in each study. Williams et al also reported the number of participants on the waitlist that were eligible to participate in their study. Adherence was described in all studies except for the one by Debette-Gratien. Morkane et al reported the number of sessions attended in those that completed the program. The study by Wallen provided the proportion of supervised and unsupervised components attended, while the study by Williams relied on self-reported diaries and weekly phone calls to determine adherence.

1.3.6.2 Safety

All studies described the occurrence of AEs, but only the studies by Wallen and Williams described how they collected this data. In the study by Williams, participants were instructed to call the study physiotherapist if they developed any AE. These were also reviewed during the weekly telephone calls of the first 6 weeks. In the study by Wallen, AEs from commencement of the study until the final study-related procedure were recorded at each session and reviewed by a physician who decided if it was related to the intervention.

1.3.6.3 Effectiveness

To determine the pre-transplantation impact of their exercise program, each study focused on a combination of endpoints including exercise capacity, anthropometry, and HRQoL. As the studies by Debette, Morkane, and Wallen included CPET assessments at baseline, they compared these

assessments with CPET values at mid- and/or end of intervention. The only CPET parameters reported in all 3 studies were peak VO_2 and peak power. The second most commonly reported exercise capacity markers included 6MWT (Debette and Wallen), and the HGS (Morkane and Wallen). All other parameters were only specific to one study. These included measures of quadriceps strength (Debette), mid-thigh pull (Wallen), incremental shuttle walk test (Williams), average daily steps (Williams), short physical performance battery test (Williams), and MAMC (Morkane). HRQoL was reported in 3 studies, but each study used a different questionnaire. The study by Debette used the short form-36 questionnaire (SF-36), while the study by Wallen used the CLQD questionnaire, and the study by Williams used the EuroQoL 5Dimension 5-Level and the hospital anxiety and depression score (HADS). Finally, the studies by Morkane, Wallen, and Williams reported post-transplant outcomes including hospital and ICU length of stay as well as survival. The studies by Debette, Morkane and Williams looked at within group differences, while the RCT by Wallen compared between groups. The assessments were conducted at the end of the 12-week intervention for the study by Debette, at the end of the 6-week intervention and 6 weeks later for Morkane, at mid-intervention week-4 and end of intervention week-8 for Wallen, and at mid-intervention week-6 and end of intervention week-12 for the study by Williams.

1.3.7 Results of the intervention

1.3.7.1 Feasibility

The study by Debette mentioned that 13 out of the 13 potential consecutive participants that met all eligibility criteria agreed to participate, meaning 100% recruitment proportion. It is not

specified how they selected those 13 participants. In the study by Morkane, 33 of the 61 patients approached were recruited into the study (54%). In the study by Wallen, 21 out of 38 eligible participants agreed to participate in the study (55%). In the study by Williams, 32 out of the 46 randomly selected individuals from the liver transplant waiting list were eligible to participate (70%). Of the 32 that were approached to participate, 18 were recruited (56%). If we incorporate eligibility and recruitment proportions as Williams et al, 39% of the randomly selected individuals on the liver transplant waiting list participated in their study. Overall, recruitment proportion was between 54-56% in 3 studies, and 100% in 1 study, or 85 out of 144 potential participants (59.0%).

Reasons for refusal to participate in these studies were reported differently for each study. In the study by Morkane, 16 out of the 28 (57%) that did not participate declined to participate, but the authors did not describe why. In the study by Wallen, 15 out of the 17 (88%) that declined to participate refused due to time and travel commitment, while this was 6 out of 14 (43%) in the study by Williams. This means that 37 out of the 59 (63%) eligible participants that refused to participate did so for logistical reasons. Other reasons for not participating included being removed from the waitlist, dying before recruitment, or receiving a liver transplant.

1.3.7.2 Adherence

Overall, 62% (8 out of 13), 56% (9 out of 16), 50% (9 out of 18), 40% (4 out of 10) of the recruited participants completed the exercise program in the studies by Debette, Morkane, Williams and Wallen, respectively. This represents 30 out of 57 (52.6%) participants. There was no obvious relationship between the duration of the intervention and completion proportion as the study

by Debette had the longest intervention and the highest completion rate. Overall, 27 participants did not complete the intervention. Reasons for lack of study completion were listed in each study and related to receiving a liver transplant (15), deteriorating clinically (6), being delisted (1), non-compliant (2), moving to another region (1), not attending (2), knee pain (1), and tibia fracture (1). Authors stated that the knee pain and tibia fracture were unrelated to study procedures[36, 39].

In terms of adherence to the exercise sessions, Morkane reported that in the 9 participants that completed the 6-week intervention, 127 out of the 135 (94%) scheduled sessions were attended. For the study by Wallen, adherence by mid-intervention at week-4 was 95% and 75% for supervised and unsupervised sessions for the 8 participants available, respectively. This was then of 100% and 88% by the end of the 8-week intervention where 4 participants remained. In the study by Williams, 82% adhered to average daily step targets and 90% to the twice-weekly functional resistance training during the first 6 weeks where participants received a scheduled weekly telephone call. Once the telephone calls stopped, adherence to the average daily steps and resistance training decreased to 53% and 78%, respectively by the end of intervention at week 12. The study by Debette did not provide information related to adherence to the exercise sessions.

1.3.7.3 Safety

In the study by Debette, 1 patient discontinued the intervention due to worsening liver disease. There was otherwise no cardiac events and no variceal bleeding or worsening of ascites. In the study by Wallen, there was 1 episode of knee injury in 236 testing and training sessions. This

episode did not lead to discontinuation of the intervention. There were no serious AEs and no episodes of variceal bleeding, or HE. In the study by Williams, one participant suffered from a tibia fracture, which was unrelated to the intervention. In the study by Morkane, 1 individual withdrew due to knee pain, which was not related to the intervention as per the authors. There was no incident worsening of cirrhosis either. Overall, 4 (7.0%) events were reported in 57 individuals who participated in an exercise program, with only 1 (1.8%) clinical deterioration, and 1 (1.8%) musculoskeletal injury related to the intervention. Prehabilitation appeared to be safe in well-selected patients awaiting liver transplantation.

1.3.7.4 Effectiveness

Three studies assessed exercise capacity by CPET, but only 2 provided within group changes (Debette and Morkane), while the other one reported between group changes (Wallen)[37-39]. There was a significant interval improvement in peak VO_2 and peak workload in 2 studies. In the study by Debette, peak VO_2 improved from 21.5 (standard deviation [SD] 5.9) mL/kg/min to 23.2 (SD 5.9) mL/kg/min (p=0.008) in those that completed the 8-week intervention. It improved from 16.2 (SD 3.4) mL/kg/min to 18.5 (SD 4.6) mL/kg/min (p<0.05) in the study by Morkane after the 6-week intervention. In the study by Debette, peak workload improved from 106 (SD 42) W to 119 (SD 45) W (p<0.02) in those that completed the intervention, while it improved from 117 (SD 26) W to 134 (SD 26) W (p<0.05) in the study by Morkane. Although the study by Wallen also included CPET parameters, they did not provide within group comparisons. Furthermore, when compared to the control group, although there were numerical improvements in peak workload (estimated mean difference of 41.6 W, 95%CI 5.9 – 77.4) and peak VO_2 (estimated mean

difference 3.2 mL/kg/min, 95%CI -2.3 – 8.7) by the end of the 8-week intervention, this did not reach statistical significance after Bonferroni correction due to multiple comparisons.

6MWT was performed in the study by Debette and Wallen. In the study by Debette, it improved from 481 (SD 69) m to 521 (SD 64) m by the end of the intervention ($p<0.02$). In the study by Wallen, there was a significant improvement in 6MWT at mid-intervention (week-4) and end of intervention (week-8) when compared to usual care. By the end of intervention, the estimated mean difference was 103.8 (95% 22.3-185.2)m, in favor of the intervention group. However, after Bonferroni correction, there was no significant between group differences. While the study by Williams did not present 6MWT, there was a significant improvement in average daily steps and the SPPB. The median daily step count increased after 12 weeks of training by 2700 steps per day compared to baseline ($p<0.01$). They also showed that the SPPB improved after 6 weeks from a median score of 9.5 to 11.5 ($p=0.02$). There was no further increase from week 6 to 12 due to ceiling effect as the maximal score is 12[36]. There was also an improvement in incremental shuttle walk test after 6 weeks of HBEP ($p=0.008$), and 12 weeks, by 470m ($p<0.01$).

Muscle strength appeared to improve after exercise training. In the study by Debette, quadriceps isometric strength improved from 30 (SD 10) kg/force to 37 (SD 13) kg/force ($p<0.008$). In the study by Morkane, HGS improved from 26.4 (SD 7.5) kg to 29.4 (SD 6.4) kg ($p< 0.05$). In the study by Wallen, there was a numerical improvement in HGS at week 4 and week 8. Authors also found a significant difference in group-by-time interaction. However, once again, after using Bonferroni correction, there was no significant between-group differences.

In terms of HRQoL, there was a general trend toward improvement in quality of life based on the SF-36 in the study by Debette. There was a numerical improvement in the global score of physical and mental health respectively, but this was not statistically significant. In the study by Williams, there was no difference in the HADS score from baseline to 6 weeks or 12 weeks. However, there was an improvement in the EuroQ5D-5L by 12 weeks, when compared to baseline with a median change of 18% (p=0.04). Specifically, there was an improvement in the proportion of patients reporting no problems with mobility and pain/discomfort.

The study by Morkane reported changes in exercise capacity in the usual care control group. As opposed to the exercise group where there was an improvement in peak VO_2 and peak workload, the control group had an interval worsening of both variables by the end of 6 weeks. Furthermore, when these measurements were repeated 6 weeks after the end of the intervention, there was a decrease in peakVO_2 in the exercise group with a return to baseline.

Post-transplant outcomes were described in the studies by Morkane, Wallen and Williams. In the study by Morkane where 7 individuals in the exercise group and 9 in the control group underwent liver transplantation, the investigators report a shorter hospital length of stay for patients in the exercise group, 13 (interquartile range [IQR] 6) days compared to 30 (IQR13) days (p=0.02). Wallen et al described that there were no between-group difference for intraoperative, perioperative or postoperative outcomes, including 90-days related mortality in those who underwent liver transplantation. Of note, only 5 patients underwent liver transplantation in the exercise group and 3 in the usual care group. No values were provided for these endpoints. In

the study by Williams, length of hospital and ICU stay in the 5 participants that were transplanted within 6 weeks of HBEP was 9 (7-14) days and 2 (1-7) days, respectively. The 7 participants that completed at least 6 weeks of HBEP had a hospital and ICU stay of 10 (5-41)days and 4 (1-10days), respectively. There were no deaths before or after transplantation.

1.4 DISCUSSION

Frailty, malnutrition, and immobility are frequent comorbidities in individuals with cirrhosis awaiting liver transplantation. This combination can be devastating as it is associated with worse outcomes before and after liver transplantation. As patients with cirrhosis can wait many months for an organ to be available, their physical status will deteriorate as their liver disease worsens[18]. The concept of prehabilitation is therefore very attractive in this patient population as there is a unique opportunity to improve their physical status ahead of a major surgery. To date, the overall feasibility, safety, and effectiveness of this intervention in patients with cirrhosis awaiting liver transplantation remains largely unknown due to scarce data. The objective of this scoping review is to review the available knowledge on this topic.

Following an extensive and exhaustive literature search, only 4 studies met all inclusion and exclusion criteria highlighting that this topic is understudied[36-39]. These studies, which were published in the last 10 years, were single center feasibility studies with a small sample size ranging from 13 to 21 participants. Only 1 study was a RCT comparing an exercise program to usual care[39]. The other 3 studies were non-randomized prospective studies where individuals participated in an exercise program, of which 1 had a non-randomized usual care comparative

arm[36-38]. The 4 studies available are very heterogeneous in terms of type of intervention, duration of intervention, and outcomes assessed. The type of intervention was largely dependent on the expertise of the center conducting the study.

At this moment, it is difficult to say whether this intervention is feasible in this patient population as participants were highly selected. For example, one study only approached those that lived within a certain radius from the hospital[37]. The proportion of patients on the transplant list that would be eligible to participate based on the long list of exclusion criteria is also unknown. Only the study by Williams looked at this and reported a 70% eligibility. As this is a single center UK study, it is unknown if this would be similar in other liver transplant center. Since these studies have been published, the guidance statement for the safe exercise training in patients with cirrhosis added other exclusion criteria, which might make it even harder to recruit patients on the waiting list[16]. In addition, the decision to participate in such a program depended on time commitment required, distance from the training facility, and general interest in the intervention. Despite some of the major differences between studies, about 30% of individuals on the liver transplant list would not be eligible and 50% of those eligible agreed to take part in a prehabilitation study. Once individuals agreed to participate, only 40-60% of them completed the intervention. Completion of the exercise program did not seem to change depending on the duration of the intervention, which ranged between 6 to 12 weeks. This could mean that only 20% of patients on the liver transplant list would participate and complete a 6-week prehabilitation program. The benefits of such an intervention might therefore only favor the few. Most common reasons for not completing the exercise program was that participants received

an organ. That being said, in those that agreed to participate, adherence to the exercise sessions was high for supervised training at more than 90% attendance[37, 39]. Comparatively, adherence seemed lower when a HBEP was proposed, with a 50 to 80% completion of scheduled sessions[36]. A possible way to palliate to this would be to include a weekly motivational call. Unfortunately, this approach is not always successful as shown in the recent STRIVE study, a multicenter pilot randomized clinical trial assessing exercise training in people with cirrhosis[42]. Despite the fact that this study included regular motivational call, adherence was very low at 14%[42]. This study was not included in the current scoping review as it did not specifically include individuals awaiting liver transplantation. Given the numbers described, it is not clear whether prehabilitation would be feasible in patients with cirrhosis awaiting liver transplantation and further studies on the subject are needed.

An important component of any novel intervention that is being evaluated is obviously related to its safety. This is particularly crucial in patients with cirrhosis awaiting liver transplantation as these individuals are particularly frail and that any significant deviation in their health status could mean that they would be ineligible for a life-saving procedure such as liver transplantation. Often, most physicians caring for patients with advanced liver disease will wait for their patients to get a liver transplantation before embarking on a major procedure with an uncertain risk to benefit ratio. Considering the 4 studies included in this scoping review, prehabilitation appears to be a safe intervention as there were no serious AEs related to the intervention. Although some participants experienced deterioration of their liver disease, study investigators did not feel it was related to the intervention[38]. However, the assessment of safety is limited as only 2 studies

had a systematic approach to identify AEs[36, 39]. Although it is possible AEs could have been missed, it is unlikely that this would have been significant as liver transplant candidates are closely followed by their treating physicians. The safety of prehabilitation was ensured by an important list of exclusion criteria. These exclusion criteria have been proposed in part by a consensus statement for the safe exercise training of patients with cirrhosis[16]. Other reviews published to date looking at the safety of exercise training in patients with cirrhosis also established that this intervention was overall safe, though the type of exercise proposed was highly variable[29, 30].

Beyond important consideration of feasibility and safety, the goal of an exercise program is to improve the exercise capacity and overall fitness of participants. This would hopefully translate into an improvement in pre- and post-transplant outcomes. At this stage, our scoping review observed mixed results. The 3 non-randomized studies showed interval improvements in multiple parameters including peak VO_2, peak workload, 6MWT, HGS, and SPPB[36-38]. The interval increase in peak VO_2 and 6MWT are considered both statistically, and clinically significant. Indeed, an increase of peak VO_2 more than 2mL/kg/min and an increase of 6MWT of more than 20m are considered clinically significant[43, 44]. Improvements were noted as early as 4 weeks after initiation of the intervention and continued until the end of the intervention, which varied between 6 weeks and 12 weeks depending on the study. These results were not replicated by Wallen et al who conducted a RCT comparing exercise training to usual care, a study design ideal to isolate the effect of an intervention. Wallen et al showed no between group differences after an 8 week intervention. As only 4 individuals were available for analysis at the end of the 8 week

intervention, the lack of difference could be related to a type 2 error because of the small sample size[39]. On the other hand, Morkane et al showed that while those who exercised had an improvement in exercise capacity, those who did not were less fit by the 6-week mark. Although this was not a randomized study, this comparative arm was composed of individuals that were matched based on age, sex, and liver disease severity[37]. This is also consistent with other prehabilitation studies that were able to show improvements in exercise capacity after 4 weeks of exercise training in a different patient group [45].

As patients who wait for a liver transplant can wait a long time after the end of an exercise program, the study by Morkane followed these patients and repeated an assessment 6 weeks after their last exercise session. They elegantly showed that the exercise capacity progressively declined back to baseline once individuals stopped exercising. This suggests that for prehabilitation to have a sustained impact on the exercise capacity of individuals awaiting liver transplantation, exercise should be maintained until the surgery. It remains to be studied whether the gains made during exercise training can be maintained until the date of transplantation.

Although we noted improvements in exercise capacity preoperatively, the impact of prehabilitation on postoperative outcomes remains uncertain. The study by Morkane suggested that the length of stay of patients who exercised was shorter than those who did not while the study by Wallen did not show any difference in length of stay, though neither studies were powered for this. Although the study by Morkane had more patients available for analysis, this

difference could be related to a type 1 error due to an unmeasured confounder. More data is therefore needed.

Lastly, prehabilitation did not lead to major changes in HRQoL. Indeed, exercise itself might not be enough to improve the HRQoL of patients with cirrhosis. A dedicated intervention aimed at relieving stress and anxiety could be more effective. Similarly, the impact of prehabilitation on the nutritional health of patients with cirrhosis is unknown. To date, the available studies did not make nutritional assessments and interventions an important aspect of trial design. We hypothesize that a multipronged approach combining exercise training, nutritional optimization, and psychological support could lead to more significant improvement of the participants exercise capacity, nutritional status and quality of life.

Our scoping review has many strengths. Although reviews have been published on the exercise training of patients with advanced liver disease, these did not focus on patients awaiting liver transplantation. We also present important feasibility, safety and effectiveness data stemming from the 4 studies identified. We also highlight important knowledge gaps to help orient future studies in the field. Our review also has limitations. Indeed, only one reviewer assessed all citations retrieved. The addition of another reviewer would ensure an important citation would not be missed. However, it is unlikely that an eligible study would have been missed for inclusion as the reviewer looked at other sources for articles including reviews on the topic. Of course, a meta-analysis would be more informative when assessing the sum effect of an intervention.

However, we do not feel that this would have been appropriate as the included studies were highly different in terms of design, intervention, and outcomes reported.

In conclusion, data on the impact of prehabilitation in patients awaiting liver transplantation is very limited and more studies are needed to appreciate whether such an intervention would be feasible, safe and effective at improving pre- and post-transplant outcomes.

CHAPTER 2

PREHABILITATION IN PATIENTS WITH CIRRHOSIS AWAITING LIVER TRANSPLANTATION: PROTOCOL OF A FEASIBILITY STUDY AND PRESENTATION OF PRELIMINARY RESULTS

2.1 INTRODUCTION

Frailty has emerged as a major predictor of worse outcome in patients with cirrhosis[46]. It is defined as a decreased physiologic reserve and increased vulnerability to health stressors that predisposes one to adverse health outcomes[47]. 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[23, 48, 49]. The presence of frailty is independently associated with waitlist mortality, while worsening LFI also predicts increased pre-transplant mortality[50,18]. Pre-transplant frailty is associated with worse post-transplant outcomes including death, hospital LOS, intensive care unit LOS, non-home discharge, and re-admission[51].

Frailty is a well-known critical issue in the surgical literature where it was shown to be a predictor of complications and death[52]. A meta-analysis comprising 683,487 patients shows the devastating impact of frailty in this patient group[53]. In their review, frailty quadruples the risk of

post-operative mortality (Risk Ratio [RR] 4.2, 95% Confidence Interval [CI] 3.0-5.9), and doubles the risk of major complications (RR 2.0, 95%CI 1.3-3.3), re-operation (RR 2.1, 95%CI 1.5-2.9), failed discharge (RR 2.2, 95%CI 1.9-2.4), and re-admission to hospital (RR 1.6, 95%CI 1.4-1.8)[53]. In addition, frailty and its associated downstream complications increase healthcare utilization and total hospital cost when compared to non-frail individuals[54]. Considering the damaging consequences of frailty, interventions have been proposed to reverse it. A network meta-analysis of 5,262 participants in RCT concludes that physical intervention alone and physical intervention with nutritional supplementation are probably the most effective at reducing frailty, and improving HRQoL measures[34]. Unfortunately, the quality of evidence is low or very low, which advocates for further clinical trials[34].

Exercise is believed to have beneficial effects in patients with cirrhosis[29]. A 2019 review of 11 studies with sample size ranging from 1 to 60 patients suggests that exercise is associated with a reduction in fatigue, and an improvement in exercise capacity, and muscle mass [29]. However, based on the results from our scoping review, only 4 studies specifically recruited patients awaiting liver transplantation, and major flaws were identified[36-39]. First, the study by Debette did not describe the type, frequency or intensity of their exercise program. This makes it difficult to replicate and confirm these findings. The second study by Williams et al. published in 2019 proposed a home-based exercise program. Although promising, this small study does not provide a supervised individualized program, which is known to be superior to home-based training as supported by a Cochrane meta-analysis of patients with intermittent claudication[55]. The study by Morkane et al. published in 2020 offered a 6-week exercise program[37]. A drawback is that they

only offered passive nutritional counseling without a directed intervention. Finally, the study by Wallen conducted a RCT comparing a prehabilitation program in patients awaiting liver transplantation to usual care. These conclusions are severely limited by the fact only 4 individuals were available at the end of the 8 week program. Despite the possible benefits of exercise training in patients awaiting liver transplantation, not a single Canadian center currently offers prehabilitation before liver transplantation[56].

2.2 OVERVIEW

As shown in the scoping review, 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.

2.3 STUDY OBJECTIVES

2.3.1 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:

- Assess the proportion of patients on the liver transplant list that would be eligible to participate in our study
- Assess the proportion of eligible participants that are recruited into the study
- Assess protocol adherence and loss to follow-up (LTFU) following study entry
- Determine reasons for refusal to participate, lack of protocol adherence or LTFU

2.3.2 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 AE during participation in the study, based on the Common Terminology Criteria for AEs v5.0 classification[62].

2.3.3 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
- 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

2.4 METHODS

2.4.1 Study design

This is an open-label single-arm feasibility prospective trial based at the McGill University Health Centre (MUHC), including the Royal Victoria Hospital, and the Montreal General Hospital. Consecutive adult patients followed at the Liver Transplant Clinic of the Royal Victoria Hospital 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 POP complex at the Montreal General Hospital.

2.4.2 Inclusion criteria

Patients with the following characteristics will be assessed for inclusion into the study:

- Age above 18 years
- Diagnosis of cirrhosis, based on clinical, laboratory, imaging, or histology findings
- Active on the liver transplant waiting list of the MUHC
- Signed informed consent form (ICF)

2.4.3 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[16]:

- MELD >20
- Hepatic decompensation within the last month (defined as variceal bleed, overt HE requiring hospitalization, uncontrolled ascites)
- High risk varices not on primary or secondary prevention
- Recurrent large volume paracentesis (at least two paracenteses in the last 4 weeks)
- Persistent HE
- Cytopenia with platelets <20,000/µL, or hemoglobin <80g/L
- Altered hemodynamics (heart rate >100bpm or <50bpm, systolic blood pressure (BP) >160mmHg or <85mmHg, diastolic BP >110mmHg or <50mmHg, oxygen saturation <92% room air)
- 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%)
- Awaiting combined organ transplantation
- Re-transplantation
- Condition limiting mobilization and/or exercise
- Recurrent falls (defined as 3 falls in the last year)

2.4.4 Study intervention: a multimodal prehabilitation program

All recruited participants will be offered a supervised prehabilitation program combining an individualized exercise program, a detailed nutritional plan, and psychological support while on the liver transplant list.

2.4.4.1 Exercise program

The exercise program is led by a team of certified physicians and kinesiologists with experience in prehabilitation. As shown below, it is structured as it has a predetermined format, and it is individualized 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 data reviewed in the scoping review and considering the average wait time for a liver transplantation. Each session will take place at the MUHC POP complex. The induction phase will include 3 sessions of 60 minutes (mins) per week for 4 weeks. The maintenance phase will then follow with a 60 mins session every other week until the date of surgery or week 24, whichever comes first. Each session will include aerobic and resistance training. The CPET is performed by a certified kinesiologist[57]. Values of workload and VO_2 at peak exercise and AT obtained from CPET will be used to deliver a high-quality individualized exercise program to each participant. The aerobic exercise is adapted from our own experience using 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[37, 58, 59]. The aerobic part will last 28 mins: 4 mins warm-up, 20 mins of HIIT on a stationary bike, and 4 mins cool-down. The HIIT will consist of 4 cycles of alternating 3 mins of moderate and 2 mins of high intensity training. The resistance training follows the aerobic training to complete 60 mins. 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[16]. 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 program. Patients will also be asked to complete a diary describing physical activity outside of the programed session that will be reviewed by the kinesiologist. This diary will be included in the patient booklet provided. 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.

2.4.4.2 Nutritional program

The nutrition program is based on current recommendations from the European Association for the Study of Liver and the European Society for Clinical Nutrition and Metabolism[60, 61]. It will be managed by a registered dietitian (RD) with experience in prehabilitation. The primary goal of our nutrition program is to correct and prevent perioperative malnutrition and support protein anabolism[62]. Patients will be assessed by the RD at baseline and categorized based on the RFH-GA tool as adequately nourished, moderately malnourished and severely malnourished[21]. Dry weight will be estimated to calculate BMI by correcting for ascites[16]. In non-obese patients, energy requirements will be estimated using indirect calorimetry and will aim for 1.2-1.4x 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. 1.2-1.5g per kg per day of protein of actual body weight). In patients with dry BMI > 30kg/m^2 (corrected for ascites), energy needs will be estimated at 65% of REE (approximately 25kcal/kg), with adequate protein intake of 2-2.5g/kg of ideal body weight,

to promote gentle weight loss. For patients with ascites, a diet containing no more than 80mmol 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, patients will be prescribed a daily multivitamin, 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 two 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.

2.4.4.3 Psychological support program

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 liver transplantation, this psychological support program was developed jointly with a local expert in such interventions.

2.4.5 Safety of participants

The safety of participants is of utmost importance. Our exclusion criteria will select participants that can safely exercise based on published guidance[16]. Previous studies are reassuring that this intervention is not associated with an unacceptable risk to participants although limited by selective outcome reporting bias[29, 30]. Exercise will be interrupted if certain specific criteria are met as per CPET international standards: angina, symptomatic arrhythmia, fall in systolic BP >20mmHg, systolic BP >250mmHg or diastolic BP >120mmHg, oxygen saturation <80% on room air, loss of coordination, mental confusion, dizziness or faintness[57]. Healthcare workers involved hold advanced cardiac life support certification and access to hospital support. AEs will be assessed by 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.

2.4.6 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. 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, of 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.

2.4.7 Study visits

Patients are screened at the liver transplant clinic. After review of selection criteria, those that agree to participate signed the ICF and received 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 4.

Table 4. 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)					

2.4.8 Study outcomes definition

2.4.8.1 Primary objective: Feasibility

Feasibility is defined as being able to recruit 20 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[36, 37, 63]. In addition, a publication from the POP group over a 5-year period of time reports an adherence of 70 to 98 % with the protocol and a LTFU of 14%[44].

2.4.8.2 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 v5.0 for grading and reporting AEs[64]. AEs will be categorized as related to the intervention or not as assessed by a study physician. Serious AEs will be defined as any AE that leads to hospitalization 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.

2.4.8.3 Exploratory objectives: Effectiveness of the intervention

We will capture a broad range of metrics influenced by our intervention based on previous studies[29]. 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 to the last pre-liver transplant values as assessed by statistical means. For frailty, we will monitor for change in LFI and proportion of frail individuals. A 0.1 change in LFI is clinically significant[18]. For exercise capacity, 6MWT, METS, peak workload, peak VO_2 will be assessed. A 14 to 30m change

in 6MWT, a 6% increase in peak VO_2 or a 1.0mL/kg/min change in peak VO_2 are considered clinically significant, but this is not validated in cirrhosis[65, 66]. For muscle mass and strength, we will assess change in HGS. Malnutrition will be assessed by a change in RFH-GA class or a change in proportion of severely malnourished individuals. Interval improvement in CLDQ will confirm the positive impact of our program on HRQoL. We will assess delisting due to death or being too unwell.

We will capture a broad range of postoperative outcomes that might improve following prehabilitation. The type, frequency, and severity of complications will be recorded and summarized using the CCI[67]. We will also record hospital LOS in days, non-home discharge (home vs not home), re-admission and mortality at 3- and 12-months.

2.4.9 Data collection

We will record baseline age, sex, gender, smoking status, alcohol consumption status, history of diabetes, etiology of liver disease, albumin, bilirubin, INR, ascites, HE, creatinine, sodium, presence of HCC, history and type of decompensated liver disease (varices, ascites, HE), history of cardiovascular disease, and history of dyslipidemia 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 pre-specified 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 as per above. HGS will be measured using a handheld dynamometer. Research personnel will follow patients throughout their time in the prehabilitation program 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- 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 program (RedCAP). Source documentation supporting the trial will be made available for trial related monitoring, audits, and institutional ethics review.

2.4.10 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 categorized 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 VO_2, 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 pre-specified visits before liver transplantation. 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 sub-group of patients that underwent liver transplantation. 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- 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 (v24.0). Reporting will be in accordance with the CONSORT guidance[63].

2.4.11 Sample size and timeline

Due to the feasibility nature of the proposed trial, a formal sample size calculation is not required[68]. As discussed previously, sample size of previous studies varies between 8 and 33

patients[36-38]. The study by Morkane et al. shows an improvement in exercise capacity and hospital LOS by recruiting only 33 patients[37]. We propose a convenient sample size of 20 patients based on the current available literature. As this is a feasibility study with potential unforeseen obstacles, it is more realistic to expect 24 months to finalize recruitment and completion of the induction phase. We will then aim to publish the initial preoperative findings within 1 year of completion of recruitment. Reporting will be according to CONSORT Guidelines for Feasibility Trials[63].

2.5 ETHICAL CONSIDERATIONS

2.5.1 Approval of study protocol

The study protocol, the ICF and relevant study documents were submitted to and approved by the MUHC Research Ethics Board (study ID 2021-7646) before study initiation.

2.5.2 Trial management

Dr. Amine Benmassaoud and Dr. Amal Bessissow will ensure proper trial conduct with the support of a trained research team. They will oversee participant enrolment, data collection, reporting of AEs and serious AEs, and data clean-up. They will ensure adherence to standard operating procedures of the McGill University Health Center Research Institute. This trial is registered at clinicaltrials.gov (NCT05237583).

2.6 FUNDING

After finalizing the study protocol, we submitted it to peer-reviewed grant funding competitions. We were successful at securing 2 grants for this study. The induction phase is funded by the Innovation Grant of the Canadian Donation and Transplantation Research Program (2021). The maintenance phase is funded by the Pilot Grant of the Canadian Association for the Study of the Liver (2021).

2.7 RESULTS

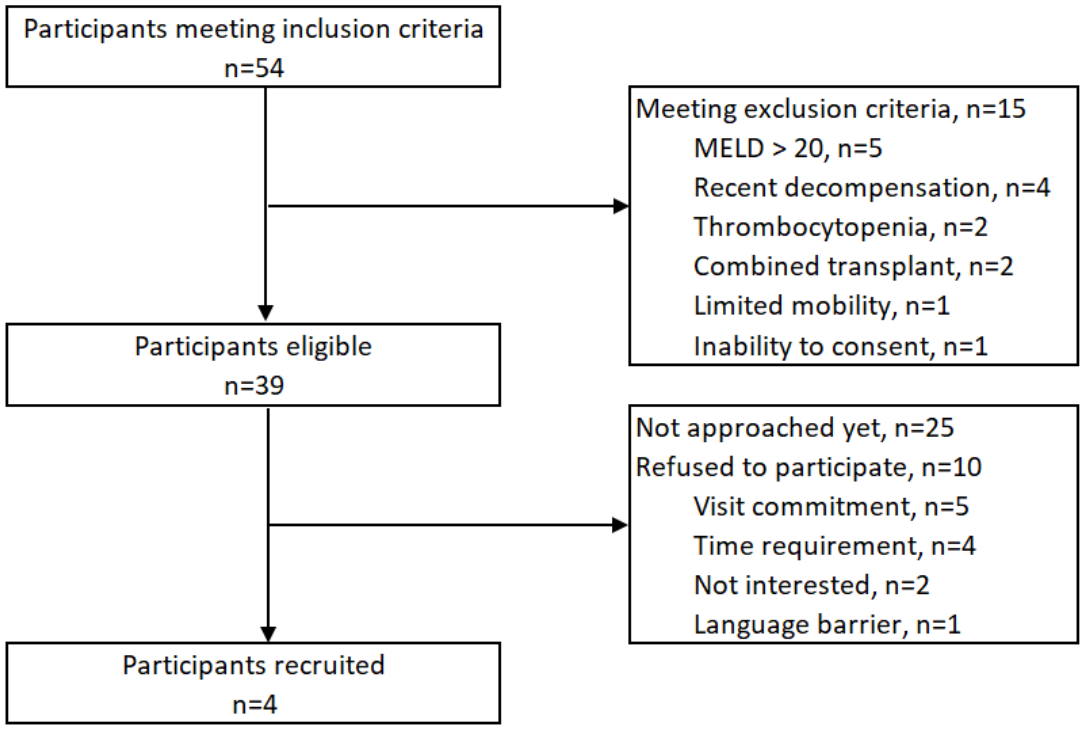
2.7.1 Feasibility

Recruitment was initiated in December 2021. The data presented herein covers the period from initiation of recruitment until October 28, 2022. Overall, 122 individuals were screened at the liver transplant clinic of the Royal Victoria Hospital, but only 54 met the inclusion criteria (Figure 2). Of those meeting inclusion criteria, 15 (27.8%) had an exclusion criteria. The most common exclusion criteria was a MELD score > 20 in 5 (33.3%), a recent decompensation in 4 (26.7%), thrombocytopenia in 2 (13.3%), listing for a combined transplantation in 2 (13.3%), limited mobility in 1 (6.7%), and inability to consent to study in 1 (6.7%). Therefore the ineligibility proportion is 72.2%.

Individuals meeting eligibility criteria were considered for participation in our study. Of the 39 eligible participants, 14 were approached by the research team while 25 will be contacted shortly. Of the 14 that were approached, 10 (71.4%) refused to participate. Reasons for refusal

included visit commitment during the induction phase in 5 (50%), time/travel requirement in 4 (40%), not interested to hear about the study in 2 (20%), language barrier in 1 (10%). Therefore 4 (28.6%) participants were enrolled in the study. To date, the first 2 participants completed the induction phase and the first half of the maintenance phase. The other 2 participants completed the baseline assessment visit and will start the induction phase shortly.

Figure 2. Participant flowchart



2.7.2 Adherence

Case 1 presented to all 3 assessment visits (100%), 11 out of 12 (91.7%) exercise training sessions during the induction phase, and 4 out of 5 (80.0%) exercise training sessions during the maintenance phase. He therefore attended 18 out of 20 sessions (90.0%). Case 2 presented to all

3 assessment visits (100.0%), 11 out of 12 (91.7%) exercise sessions during the induction phase, and 4 out of 5 (80.0%) sessions during the maintenance phase. He therefore attended 18 out of 20 sessions (90.0%). Case 3 and 4 both attended their initial assessment visit (100%). Therefore, overall adherence to the induction phase is 22 out of 24 (91.7%) exercise sessions, while in the maintenance phase, it was 8 out of 10 (80.0%) sessions, based on the 2 cases that participated thus far.

2.7.3 Safety

Case 1 participated in a total of 15 exercise sessions and 3 assessment visits. He experienced no AE. Specifically, there was no hepatic decompensation related to portal hypertension, including ascites, variceal bleeding, or HE, no cardiovascular event, and no musculoskeletal events. Although his MELD score increased from 17 at baseline to 20 during his participation, this was not felt to be related to the intervention but rather to his resumption of alcohol consumption. Because of this, he was put inactive on the liver transplant list and was removed from the study. Case 2 participated in a total of 15 exercise sessions, and 3 assessment visits. His participation was halted after the assessment mid-way through the maintenance phase due to worsening symptoms from a known abdominal hernia. Although his symptoms did not initially prohibit him from participating in the program, they worsened and he was no longer able to participate. This was considered as a possible non-serious AE related to the intervention. Otherwise, he did not experience any other AEs, including no hepatic, cardiovascular, or musculoskeletal AEs. Case 3 and 4 experienced no AEs during their assessment visits. Overall, there was 1 AE possibly related

to the intervention over a total of 38 visits (2.6%), or over a total of 2 participants that underwent exercise training (50%).

2.7.4 Effectiveness of the intervention

Considering that only 4 individuals have been recruited into the study, the data related to the effectiveness of the intervention will be presented as a series of case presentations. A summary of the baseline characteristics is included in Table 3. Longitudinal data for those who have participated in at least 1 re-assessment is presented in Table 4. Of note, no one was delisted for being too unwell, no one died, and no one has received a liver transplant.

Case 1

Case 1 was a 61 year old male known for decompensated alcohol-related cirrhosis with ascites controlled on diuretics, HE controlled on lactulose, and varices on carvedilol for secondary prevention of bleeding. At baseline, his MELD score was 17 and his Child-Pugh (CP) score was C-10. His BMI was 27.5kg/m^2, and his mid-upper arm muscle circumference was 19.8cm placing his below the 5^{th} percentile for age and sex. His dominant HGS was 24.3kg. His LFI was 3.92, classifying as pre-frail and at the 61^{st} percentile. His 6MWT was 384m. CPET assessment revealed a peak power of 97W, a peak VO2 of 16mL/kg/min, and an ability to perform 4.6METS. His protein and caloric intake at baseline met 56% and 79% of his expected needs, respectively. Overall, he was considered moderately malnourished by the RFH-GA. As per CLDQ, his overall score was 3.4.

During the induction phase, he attended 11 out of 12 sessions (91.7%) and had no AEs. At the assessment at the end of the induction phase, his MELD increased to 20 and CP score was C-11. His BMI was 27.2kg/m^2 and his MAMC remained below 5th percentile. His HGS increased slightly to 24.6kg, while LFI deteriorated slightly to 4.18 (pre-frail category, 72nd percentile). His 6MWT increased significantly to 423m. CPET revealed stable peak power (97W), a decreased peak VO2 (14.2mL/kg/min), and only able to perform 4 METS. His nutritional intake remained stable at 56% of his protein needs, and his remained as moderately malnourished as per RFH-GA. CLDQ improved to 4.3. Although some of the results showed improvement, the CPET suggested a worse exercise capacity. On the day, the patient smelled of alcohol. He was asked about alcohol consumption which he denied.

During the maintenance phase, he attended 4 out of 5 sessions (80.0%), and developed no AEs. At the assessment mid-way through the maintenance phase, his MELD was stable at 20 and his CP score was stable at C-11. His BMI decreased further to 25.4 as he lost 5.5kg since last visit. His MAMC remained below 5th percentile. His handgrip continued to improve to 27.7kg and his LFI improved to 3.87 (pre-frail at 48th percentile). His 6MWT remained higher than baseline at 426m. CPET showed improved peak power at 103W, peak VO2 at 16.9mL/kg/min, and METS at 4.8. Although his nutritional assessment showed he was still moderately malnourished, he significantly improved his protein and caloric intake at 79% and 135%, respectively and therefore classified as adequate. CLDQ was 3.7, with consistent improvement only noted in the worry sub-domain.

During a medical visit with his primary treating hepatologist, he was noted to have returned to alcohol consumption. He was therefore removed from the study after the assessment above. He was also removed from the transplant waiting list while he is re-assessed by the transplant psychiatrist. This was not related to the study intervention.

Case 2

Case 2 was a 64 year old male known for decompensated alcohol-related cirrhosis with ascites controlled on diuretics, and HE controlled on lactulose. At baseline, his MELD score was 8 and his Child-Pugh score was B-7. His BMI was 18.3kg/m^2, and his mid-upper arm muscle circumference was 19.8cm placing his below the 5th percentile. His dominant HGS was 28.7kg. His LFI was 3.84 (pre-frail, 48th percentile). His 6MWT was 354m. CPET assessment revealed a peak power of 107W, a peak VO2 of 17.3mL/kg/min, and an ability to perform 5.0METS. His protein and caloric intake at baseline met 45% and 51% of his expected needs, respectively. Overall, he was considered severely malnourished by the RFH-GA. As per CLDQ, his overall score was 5.8.

During the induction phase, he attended 11 out of 12 sessions (91.7%) and had no AEs. At the assessment at the end of the induction phase, his MELD was overall stable at 9 and CP score was B-7. His BMI improved to 19.2kg/m^2 and his MAMC remained below 5th percentile. His HGS increased slightly to 29.0kg, while LFI was stable at 3.83 (pre-frail category, 48th percentile). His 6MWT increased significantly to 424m. CPET revealed stable peak power at 105W, an improved peak VO_2 at 18.6mL/kg/min, and he was able to perform 5.3 METS. His nutritional intake

improved significantly now meeting 83% and 102% of his protein and caloric needs, respectively. He improved from severely to moderately malnourished. CLDQ was stable at 5.5.

During the maintenance phase, he attended 4 out of 5 sessions (80.0%). He described worsening abdominal pain related to his abdominal hernia. Although initially it did not prevent participation in the program, he stopped participation after the assessment mid-way through the maintenance phase. This was therefore considered as a non-serious AE (abdominal pain) possibly related to the intervention. At visit 20, his MELD was stable at 9 and his CP score was stable at B-7. His BMI decreased 17.9kg/m^2 as he lost 6kg since last visit. His MAMC remained below 5th percentile. His handgrip was not reliable, so neither was his LFI. His 6MWT decreased from end of induction, but was still higher than at baseline at 390m. CPET showed worsening with peak VO2 at 16.6mL/kg/min, and only able to do 4.7 METS. These values were worse than at baseline. His peak power was stable at 105W. Nutritional assessment revealed a return to a near baseline inadequate protein and caloric intake at 38% and 76%, respectively. He was therefore considered severely malnourished. Simultaneously, CLDQ worsened to 3.2 with a decrease score in all sub-domains, from abdominal symptoms, fatigue, systemic symptoms, activity, emotional function, and worry. He did not complete further exercise sessions due to worse abdominal pain related to the abdominal hernia.

<u>Case 3</u>

Case 3 was a 49 year old female known for decompensated primary biliary cirrhosis with ascites controlled on diuretics, and variceal bleeding requiring a TIPSS insertion. At baseline, her MELD

score was 7 and his Child-Pugh score was A-5. Her BMI was 17.8kg/m^2, and her MAMC was 15cm (< 5^{th} percentile). Her dominant HGS was 18.7kg, and an LFI of 3.90 (pre-frail, 48^{th} percentile). Her 6MWT was 572m. CPET assessment revealed a peak power of 134W, a peak VO2 of 23.0mL/kg/min, and an ability to perform 6.6METS. Her protein and caloric intake exceeded her needs at 146% and 143%, respectively. As her BMI and MAMC were low, despite her adequate intake, she was considered to be moderately malnourished. She also had very good quality of life with CLDQ 6.4. No AEs related to assessment visits were noted.

Case 4

Case 4 was a 60 year old male known for decompensated alcohol-related cirrhosis with ascites controlled on diuretics, and variceal bleeding requiring a TIPSS insertion. At baseline, his MELD score was 8 and his Child-Pugh score was B-7. His BMI was 19.9kg/m^2, and his MAMC was 19.0cm (< 5^{th} percentile). His dominant HGS was 24.3kg, and his LFI was 3.79 (pre-frail, 48^{th} percentile). His 6MWT was 525m. CPET assessment revealed a peak power of 110W, a peak VO2 of 20.2mL/kg/min, and an ability to perform 5.8METS. His protein and caloric intake exceeded his needs at 129% and 180%, respectively. As his BMI and MAMC were low, he was considered to be moderately malnourished. Total CLDQ score was 4.9. No AEs related to assessment visits were noted.

Table 5. Summary of baseline characteristics of patients recruited

Variables	Total cohort, n=4
Age (mean, SD)	58.5 (6.6)
Male:Female Sex (%:%)	3:1, (75:25)
Etiology of Liver disease	
Alcohol-related liver disease	3 (75%)
Primary Biliary Cirrhosis	1 (25%)
Decompensated cirrhosis	4 (100%)
Hepatocellular carcinoma	0 (0%)
Body mass index, in kg/m^2 (mean, SD)	21.1 (4.3)
MELD score (mean, SD)	10.0 (4.7)
Child Pugh score	
A	1 (25%)
B	2 (50%)
C	1 (25%)
6 minute walk test, in meters (mean, SD)	458.8 (106.1)
Handgrip strength, in kg (mean, SD)	24.0 (4.1)
Liver frailty index score (mean, SD)	3.86 (0.06)
Liver frailty index categories	
Pre-frail	4 (100%)
Frail	0 (0%)
Royal Free Hospital-Global Assessment	
Moderately malnourished	3 (75%)
Severely malnourished	1 (25%)
Peak workload, in watts (mean, SD)	112.0 (15.7)
Peak VO_2 , in mL/kg/min (mean, SD)	19.1 (3.1)
METS (mean, SD)	5.5 (0.9)
Chronic Liver Disease Questionnaire (mean, SD)	5.1 (1.3)

Legend: MELD = model for end-stage liver disease score, METS = metabolic equivalents, SD = standard deviation.

Table 6. Change in pre-operative metrics in participants with repeat measurements (n=2)

	Baseline (mean, SD)	Week 5 (mean, SD)	Difference vs baseline	p-value	Week 15 (mean, SD)	Difference vs week5	p-value
6MWT, m	369.0 (21.2)	423.5 (0.7)	+54.5 (21.9)	0.18	408.0 (25.5)	-15.5 (26.2)	0.66
HGS, kg	26.5 (3.1)	26.8 (3.1)	+0.3	0.16	--	--	--
LFI	3.9 (0.1)	4.0 (0.2)	+0.1 (0.2)	0.66	--	--	--
PeakVO2, mL/kg/min	16.7 (0.9)	16.4 (3.1)	-0.3 (2.2)	0.66	16.8 (0.2)	+0.4 (3.3)	0.66
CLDQ	4.6 (1.7)	4.9 (0.8)	+0.3 (0.8)	0.66	3.5 (0.4)	-1.5 (1.2)	0.18

Legend: 6MWT = 6minute walk test, CLDQ = Chronic Liver disease questionnaire, HGS = handgrip strength; LFI = Liver Frailty Index

CHAPTER 3

FEASIBILITY OF PREHABILITATION IN PATIENTS WITH CIRRHOSIS AWAITING LIVER TRANSPLANTATION: DISCUSSION

3.1 DISCUSSION

The development of decompensated cirrhosis leads to a significant increase in morbidity and mortality where the only life-saving treatment is liver transplantation[69]. While the liver transplant list prioritizes individuals based on medical urgency, many patients wait weeks to months before they receive an organ. During this period of time, individuals with cirrhosis become at higher risk of frailty, malnutrition and low muscle mass. This state of heightened physiologic vulnerability further compounds their chance of a worse outcome. Although preliminary evidence suggests that exercise training is safe in patients with liver disease, the impact of this intervention on patients with cirrhosis on the waiting list is still unknown[31].

We present herein the early data from our feasibility study. In terms of eligibility, we note a similar proportion of individuals on the transplant list that are eligible to participate in our prehabilitation program when compared to the study by Williams[36]. In their study, 70% were eligible, while it is 72% in our study[36]. A common reason for not being eligible is a high MELD score, a criteria not integrated in the earlier studies. A major difference thus far is that our recruitment proportion is 28.6% (4 out of 14 participants approached), as opposed to 59.0% for

the studies included in our scoping review. The most common reasons for refusal to participate are visit commitments and time/travel requirements. Although our induction phase is very similar to the study by Morkane or Debette who had 3 and 2 supervised sessions per week for 6 and 12 weeks, respectively, their recruitment proportion was 54% and 100%, respectively[37, 38]. This discrepancy could be due to the low number of participants that we have approached thus far. Another explanation could be that our recruitment proportion is more representative of unbiased approach to participant recruitment. Indeed, as we are a referral center for a very large area, patients assessed at our clinic can live up to 2 hours away from the hospital and we have approached all patients followed at our clinic. On the other hand, the study by Morkane only approached individuals that lived close to the hospital, while the study by Debette did not describe how they selected the 13 participants that participated in their study[37, 38].

At this stage, 2 participants have completed the study after reaching week 15, meaning mid-way through the maintenance phase. The first one was removed as he returned to alcohol consumption, while the second did not continue due to symptoms of abdominal pain related to an abdominal hernia.

During their time in the study, they showed a very high adherence rate for the induction and the maintenance phase. Overall, adherence to the induction phase was 22 out of 24 sessions (91.7%), while in the maintenance phase it was 8 out of 10 (80%). Furthermore, combining all 38 sessions conducted, there were no AEs related to a cardiac, musculoskeletal or hepatic cause. There was

only 1 case of a non-serious AE related to the exercise program, specifically abdominal pain from known abdominal hernia. This led to Case 2 to stop its participation in the study.

By the end of the induction phase at week-4, both participants experienced improvements in 6MWT. The degree of improvement noted in their 6MWT is considered clinically significant. As Case 1 had returned to alcohol, his CPET values might be unreliable. For Case 2, there was a clinically relevant improvement in oxygen consumption at peak exercise. Similarly, he followed the dietician's advice and improved his nutritional status from severely malnourished to moderately malnourished as per RFH-GA. Despite this, there was no improvement in his LFI which was stable in the pre-frail category. Overall, the induction phase led to improvements in 6MWT after only 4 weeks of training. These improvements are consistent with a previous study where the exercise capacity of patients undergoing prehabilitation improved as early as 4 weeks after training initiation[45, 70]. Our study design and intervention are therefore appropriate to see rapid improvements in exercise capacity.

By the middle of the maintenance phase at week 15, both patients experienced a significant decrease in weight. For Case 1, his weight loss can be partly explained by a return to alcohol consumption which can impact nutrient intake and absorption and worsen a pro-inflammatory and catabolic state. In addition, he did not increase significantly his protein and caloric intake despite advice from the dietician. At baseline, Case 1 was overweight but also had a low muscle mass as highlighted by a MAMC below the 5th percentile. The weight loss he experienced likely induced a loss of both adipose and muscle mass. For Case 2, the weight loss occurred during a

period where he was troubled by his abdominal hernia which also caused worse quality of life including increased worries and emotional distress as highlighted by the CLDQ questionnaire. His appetite was also affected as highlighted by a decrease in protein and caloric intake no longer meeting his needs. While both cases were instructed and provided with nutritional supplements to take regularly and during exercise sessions, motivation and consistent use of these supplements were lacking. It is possible that the exercise routine itself led to weight loss especially if catabolic activity induced by exercise was not compensated by adequate anabolic supplementation with proteins and calories. Prehabilitation programs that induce significant energy expenditure should incorporate an active nutritional assessment and optimization strategy. This is particularly important for individuals whom at baseline do not meet their nutritional goals, which is common in patients with cirrhosis awaiting liver transplantation.

Our multimodal prehabilitation program is driving significant changes in the participant's condition, from exercise capacity, nutritional status and quality of life. At week 15, the exercise capacity of Case 1 and Case 2 remained better than at baseline. Case 1 had better 6MWT and peak VO_2 compared to baseline, while for case 2, it was only the 6MWT. The LFI and MAMC did not show significant response to the intervention thus far. The RFH-GA showed responsiveness to the intervention as it improved for Case 2, before worsening again. This fluctuation mirrored his protein and caloric intake. The CLDQ questionnaire which assessed quality of life was highly responsive to patient overall condition as shown by a sharp decrease for Case 2 who had issues with his hernia. Furthermore in Case 1, the worry sub-domain improved consistently during the intervention which could suggest a direct impact from the consultation for anxiety reduction. A

recent systematic review attempted to identify which pre-liver transplant tools that assess functional capacity, frailty, and muscle mass can stratify patients risk of adverse post-transplant outcomes[70]. This review identified 22 studies, including 6 prospective studies, that evaluated tools such as LFI (3 studies), 6MWT (1 study), CPET (2studies), and Sarcopenia by CT (11 studies). Authors concluded that there was moderate quality evidence that LFI, Sarcopenia by CT, and CPET can identify patients at low risk of complications post liver transplantation and therefore suitable for enhanced recovery pathways. It remains to be seen which tools predict outcomes pre or post-transplantation after participation in a multimodal prehabilitation program.

Our study has many strengths as it attempts to answer major questions related to the feasibility, safety, and effectiveness of prehabilitation in patients awaiting liver transplantation which have been highlighted by the ATS and CST in a very recent consensus statement[31, 32]. In addition, our protocol and clinical trial was developed after a thorough review of the literature. Our scoping review identified significant knowledge gaps which we attempt to address in the study design itself. Furthermore, our group has a lot of experience conducting clinical trial on prehabilitation. This experience was adapted to the reality of patients with liver disease by working jointly with a strong multidisciplinary team. This exceptional collaborative effort will ensure a successful clinical trial. Furthermore, we consciously chose to only include patients with cirrhosis on the waiting list as they are often more frail and malnourished than patients without cirrhosis. For example, a patient with polycystic liver disease does not have the same degree of synthetic liver dysfunction or portal hypertension as a patient with decompensated cirrhosis. Patients without cirrhosis on the transplant waiting list would respond differently to a prehabilitation intervention

than those with cirrhosis simply because of differences in hepatic physiology. Finally, we will record a wide range of parameters expected to change with exercise training, nutritional optimization, and psychological support. This will allow us to identify which parameters can predict pre- and post-transplant outcomes in individuals who have undergone multimodal prehabilitation.

The study also has several limitations that deserve to be acknowledged. Firstly, it is very difficult to draw any robust conclusions as the sample size is very small. Our study is still active and will continue to recruit more participants. We hope to reach our intended sample size in the near future. Unfortunately, the global COVID-19 pandemic has hindered our efforts considering these participants are at high risk of morbidity and mortality if they contract COVID-19. For this reason, we have taken the necessary precautions to decrease the risk of transmission by using personal protective equipment, encouraging telephone visits when possible, and staggering recruitment. Secondly, our study relies on supervised exercise sessions. This might not reproducible in all other liver transplant centres. Although local resources are important to consider when implementing an intervention, the evidence to date suggests that a supervised setting is better than an unsupervised one[55]. The supervised setting has been associated with higher adherence and it was shown to be more impactful on exercise capacity than unsupervised training. Thirdly, as a single arm study lacking a comparator, it will be difficult to know if changes in exercise capacity would have been noted regardless. However, this is unlikely as patients with cirrhosis tend to get weaker as time goes by on the waiting list. As shown in a multicentre study following 1093 individuals with cirrhosis eligible for liver transplantation, 49% of patients had at least moderate

worsening of frailty, while only 16% had an improvement in frailty[18]. As a single centre study, it will lack the generalizability and external validity necessary to extrapolate our findings to other liver transplant centres. Indeed, liver transplant centres can have very different patients on their waitlist. Differences can range from cause of liver disease, availability of organs, to distance the liver transplant candidate lives from a hospital. These can have an impact on the feasibility, safety, and effectiveness of our intervention. To favor generalizability, we propose a highly individualized exercise program based on each person's ability to exercise. Our HIIT program uses data from the baseline CPET to determine the intensity of the exercise regimen. Some of these limitations are commonly seen in feasibility studies. However, at this moment, a feasibility study is the best study design for this intervention in this patient population. More data needs to be generated before carrying a larger definitive trial.

In conclusion, very preliminary results from our study shows that our intervention is safe and associated with high adherence. Improvements in exercise capacity have been noted in the first 4 weeks and these remained better than at baseline during the maintenance phase. If our intervention does improve exercise capacity while being feasible and safe, the newly generated data will be used to calculate the necessary sample size to show a difference in a subsequent larger trial.

CHAPTER 4

CONCLUSIONS AND FUTURE DIRECTIONS

4.1 CONCLUSIONS

Individuals with cirrhosis awaiting liver transplantation are often malnourished, sarcopenic, and frail. This decreased physiologic reserve leads to an increased risk of poor outcome both before and after liver transplantation. While exercise training appears to be safe in patients with advanced liver disease, none of the Canadian liver transplant centers offer this potentially beneficial intervention to their patients on the waiting list. Correcting malnutrition, sarcopenia or even preventing worsening of frailty could decrease their risk of complications. It is therefore important to optimize the fitness of patients with cirrhosis on the waiting list.

Although the current literature suggests that it is feasible and safe for patients awaiting liver transplantation to participate in an exercise program, most of the studies were of small sample size and assessed very different interventions. Building on the existing knowledge gaps in the field, our study was developed to provide patients and clinicians with a prehabilitation program capable of improving the fitness of individuals with cirrhosis awaiting liver transplantation. The current study which focuses on feasibility, safety, and effectiveness of a multimodal prehabilitation program is still active and recruiting. Based on our limited experience thus far, we have shown that our intervention is safe with no occurrence of serious AEs. Although recruitment

has been low compared to previous studies, it could be more representative of reality when all eligible individuals are offered to participate in a supervised prehabilitation program. Once patients started the intervention, the adherence was high. In terms of effectiveness, we cannot draw definite conclusions based on the very small sample size.

Altogether, we believe that our intervention has the potential of being successful at achieving its initially stated goals. Our study will continue to recruit participants until we meet our sample size target. A full publication will then be submitted for peer review.

4.2 FUTURE DIRECTIONS

Based on our current experience and evidence accrued to date, a multimodal prehabilitation program combining exercise training, nutritional optimization, and psychological support has the best chance to positively impact the pre- and post-transplant outcomes of patients with cirrhosis awaiting liver transplantation. Future studies should look at the generalizability of our findings and correct for unaccounted for biases by conducting a randomized controlled trial recruiting across all Canadian liver transplant centres stratifying based on the degree of frailty, sarcopenia, or malnutrition. This will also allow us to identify which individuals derive the most benefit from such an intervention. We might find that robust individuals derive less benefit from prehabilitation than those that are frail. Incorporating a cost-effectiveness analysis will also inform decision making and whether it is important to implement such a program. Preliminary talks will soon be organized with the main stakeholders across the country.

APPENDICES

Appendix 1. Participant instruction booklet

Appendix 2. Procedure instruction booklet

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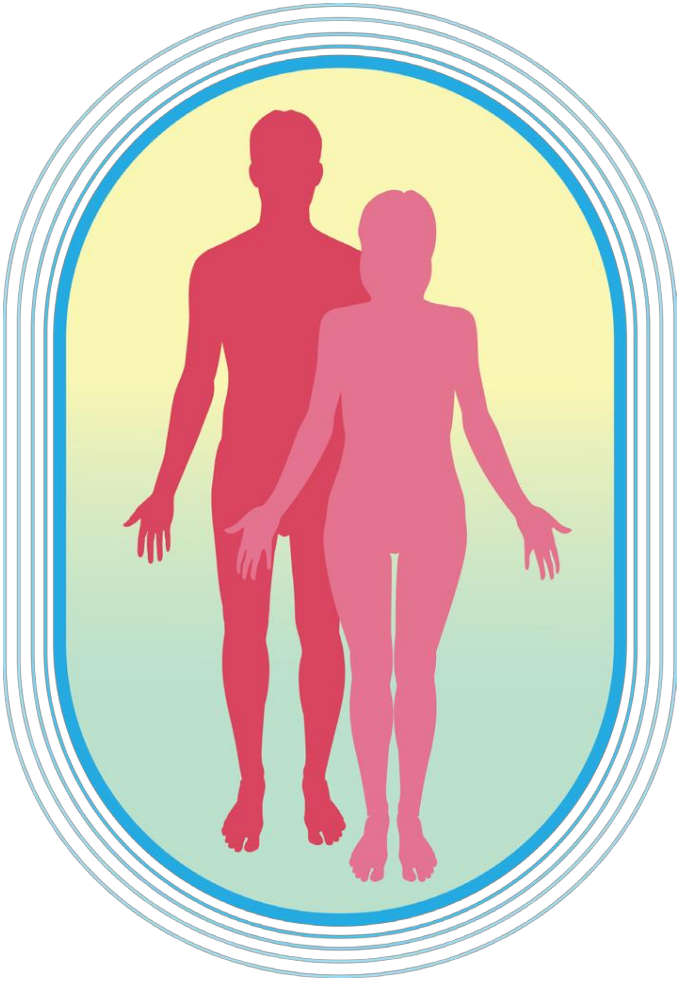
PREHABILITATION BEFORE LIVER TRANSPLANTATION



Participant booklet

Centre universitair
de santé McGi

Personalized prehabilitation for individuals awaiting liver transplantation

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Version number: 1.1

Centre universitaire de santé McGill

McGill University Health Centre

Dear Mr, Mrs,

Thank you for choosing to be part of our Prehabilitation for Liver Transplantation study. This is a study to determine whether there are added benefits in terms of accelerated recoverytime and decreased complication rates when patients are active and have good nutritional and mental status prior to their liver transplantation. In this booklet you will find informationregarding Prehabilitation and what is expected of you during this study.

We are a group of hepatologists, hepatobiliary surgeons, anesthesiologists, internists, nurses, physiotherapists, kinesiologists,nutritionists, and psychologists. We will all work together to make this an enjoyable experience for everyone involved. The intent of this program is to improve your ability to cope with stressful situations, to gain muscular strength and aerobic endurance, and to improve your nutritional status prior to surgery.

If you have questions at any time throughout this study, please donot hesitate to contact me, or one of the project coordinators. We will be happy to respond to any questions or concerns you may have.

Thank you very much for your time and cooperation in this study.

Sincerely,

Dr. Amine Benmassaoud
Principal Investigator
Department of Medicine
Royal Victoria Hospital

Contacts: .....

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Table of Contents

Your Guide to Prehabilitation

What does Prehabilitation Involve?

After a study visit, you will meet with a kinesiologist who will describe exercises that you will do during your participation in the study. During these study visits your body strength, nutritional state, and mood will be assessed by the research staff. You will also be asked to answer a few questionnaires.

The following is a brief overview of the programs:

A Physical Activity Program

- The kinesiologist will prescribe a personalized exercise program that you will perform 3 times per week for the first four weeks, then once every two weeks for a total of 24 weeks. The program might stop earlier if you have your liver transplantation before then.

A Nutrition Program

- The nutritionist will provide advice on optimal nutrition and prescribe nutritional supplements as needed.

Psychosocial Program

- The psychosocial nurse will help reduce stress and anxiety before the procedure as needed.

Measurements

- The Research staff will assess your strength, mood, and nutritional state regularly during your participation.

Prehabilitation Schedule

Prior to Surgery

You will be contacted by the project coordinator who will arrange your initial study visit with the kinesiologist and a nutritionist. At this visit, your physical strength, mood, and nutritional state will be assessed. At the next visit, you will return to the Preoperative Program Centre to start exercise training. You will have 3 sessions per week for 4 weeks followed by one session every two weeks until week 24. You will also be asked to keep track of your physical activity outside of the programby writing in the "log" section of this booklet. Remember, if you have any questions, please do not hesitate to contact the research team. Your progress will be monitored during in-person visits.

During hospitalization for surgery

During your hospitalization for liver transplantation, the research team will collect information regarding your progress. You will not need to be directly involved as this will be done through chart review.

3 months after surgery

At 3 months after your surgery for liver transplantation, the research team will collect further information related to your general health. You will not need to be directly involved as this will be done through chart review.

12 months after surgery

At 12 months after your surgery for liver transplantation, the research team will collect further information related to your general health. You will not need to be directly involved as this will be done through chart review.

Nutritional Program

A nutritionist is a health professional who teaches you about food and nutrition.

He or she will assess your nutritional state, what you eat regularly, your appetite, weight loss, and your likes and dislikes.

Why is healthy eating important?

There are many benefits of eating well. The list below gives you an overview of some of these benefits:

- Helps your body to fight off infection.
- Keeps your muscles and bones strong.
- Helps maintain strength and energy to participate in activities that you do every day
- Helps maintain a healthy weight.
- Increases energy and fuels your physical activities such as walking.
- Improves your mental health.

Take steps towards a well-balanced diet

Eating well means including a variety of foods to provide your body with the nutrients you need to maintain health, feel well, maintain a healthy weight, and have good energy. Including a variety of foods helps provide your body with adequate amounts of calories, protein, fat, carbohydrate, fluid, vitamins, and minerals. The table below outlines the valuable role of these nutrients:

Nutrients	**Roles**	**Examples of Food Sources**
Calories	Fuel our body and all of its functions.	All foods provide calories
Proteins	The building blocks of all of the body's tissues, including muscle. Supports maintenance, growth, and repair of all of the body's tissues. Keeps your immune system healthy.	Meat, poultry, fish, seafood, eggs, dairy, nuts & seeds, soy, pulses/legumes
Fats	A rich source of calories. Helps the body grow and produce new cells and hormones. A good source of vitamins: A, E, D, and K.	Oils, butter, nuts, eggs, dairy
Carbohydrates	Gives quick energy. Acts as the main energy source for all cells in the body, and is the only fuel source for the brain. It's a good source of adding fiber in your diet.	Fruits, starchy vegetables, bread, pasta, grains, cereals, crackers and legumes (beans, peas lentils)
Fluids	Transports nutrients through the body, maintains proper functioning of the digestive tract, and gets rid of waste.	Water, broth, milk, fruit or vegetable juices, sports drinks, tea
Vitamins and Minerals	Does hundreds of different roles in the body, including maintaining bone health, helping heal wounds, maintain/strengthen the immune.	All foods give you some vitamins and minerals, but some foods give you more than others. These nutrient-rich foods are: vegetables, fruits, nuts, seeds, whole grains, dairy and legumes.

Here are some tips to maximize your nutritional health:

o **Eat balanced meals**. See the "Plate Method" on the last page. The Plate Method is designed to help you easily meet your nutritional needs. As an example, 1⁄4 of your plate should include carbohydrate-rich foods to provide you with energy and B-vitamins.

o **Include a variety of different colours of vegetables and fruits**. Fruits and vegetables with bright colours are nutrient- and antioxidant-rich foods. Aim to eat dark green, red, and orange vegetables and fruits on a daily basis.

o **Include high fiber** foods such as whole grains (barley, bulgur, millet, oats, quinoa, rye) and legumes (beans, peas and lentils).

o **Eat high-protein meals.** Include protein-rich foods at every meal and snack.

o **Aim to eat fish 1-2 times per week.** Salmon, tuna and trout are rich in omega-3 fatty acids. These healthy fats help to lower stress in your body.

o **Avoid prepackaged and processed foods**. Processed foods are packaged foods such as frozen meals or boxed foods. They can contain a lot of sodium.

o **Avoid refined grains,** such as white bread, and sugary beverages

o **Limit red meats** (beef, pork, lamb, etc.) to no more than 500g (18oz) /week and avoid processed meats (bacon, deli meats, etc.).

o **Avoid alcohol and eat low-sodium foods.** You should consume less than 2g of sodium per day, the equivalent of 1 teaspoon (2.3g of sodium).

Malnutrition: What is it and how do know if you're at risk ?
Anyone can become malnourished or at risk of being malnourished when their food does not meet their body's needs. Your nutrition needs can change as you get older, when you're living with a disease, or when you're going through treatment. You can screen yourself for malnutrition and play a big role in your health. Some signs to look out for:

- Eating less than is normal for you.
- Losing weight without trying.
- Experiencing side-effects of treatment or other symptoms that make eating difficult, such as poor appetite, feeling full quickly, nauseous (feeling that you want to throw up) or having difficulty swallowing foods.
- Always reach out to your clinic doctor if you are concerned that you are becoming malnourished.

<u>If you are malnourished, losing weight or have a poor appetite</u>, we suggest:
o **Eat small frequent meals every 2-3 hours when awake.**

o **Choose a protein source** at all (or most) meals and snacks. It is best to space out protein foods, rather than eating one large serving at once, to keep your muscles fed and strong throughout the day. Most people don't eat enough protein with breakfast, so try adding 1-2 high protein foods such as yogurt, cheese, milk, and eggs.

o **Choose calorie-rich foods** at all (or most) meals and snacks to help make every calorie count. Ways to increase the overall calories in your meals include higher fat dairy products, avocado, nut butters, and homemade dressings or sauces. Make sure to watch the salt content!

o **Include a variety of foods** to the best of your ability. If you are concerned that you are not including all the essential vitamins and minerals, a multivitamin may be right for you. Always speak with your clinic doctor before starting any supplements.

o **Food is medicine**. If you have difficulty eating well, speak with your clinic doctor.

o **Have a late evening snack 1-2hrs before bed.** You should also have a snack if you wake up in the middle of the night. It should contain 50g of complex sugars (e.g. 1 bottle of high calorie nutritional supplement).

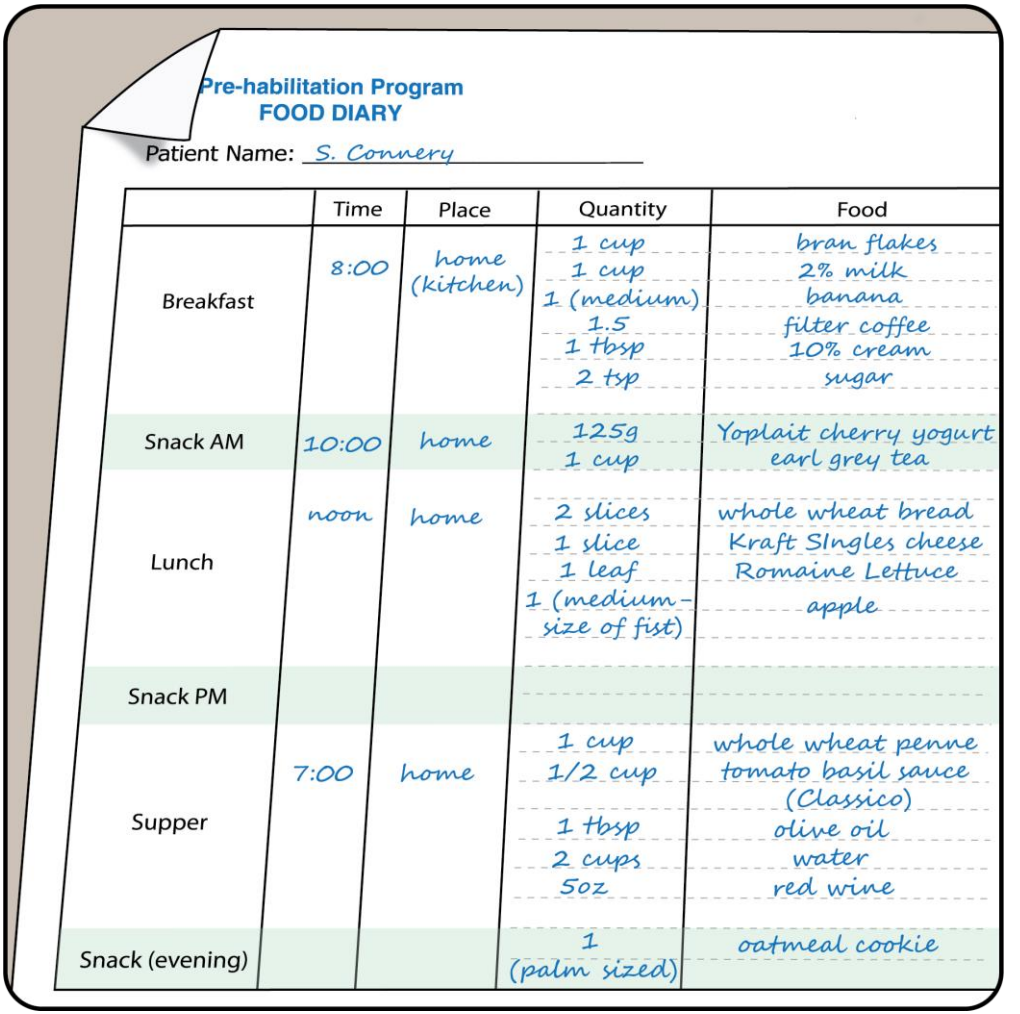
Why is it important to eat well before, during, and after surgery?
Your body needs proteins, vitamins A, C, D, E as well as calcium, zinc, and iron to heal well. Before surgery, you can prepare your body to heal well by eating enough (using the tips we have given you) to avoid lacking nutrients and even build a small reserve. After surgery, your body will rely on this reserve and the food you eat to heal well.

Recording what you eat in your food diary

You will be asked to keep a diary of everything you eat and drink for 3 days (2 weekdays and 1 weekend day). This will include **ALL** foods, supplements, and liquids that you eat or drink over this *3 day* period. Be as specific as you can. Write down brand names and the amounts you eat or drink. You can use our serving size guide to help you figure out how much you eat or drink. Tofill out your food diary precisely, you may also measure all your food and beverages with measuring cups and spoons at home. The nutritionist will ask you to bring in your diary during follow-up visits. If you have any questions, the nutritionist will gladly answer them for you.

- Write absolutely everything that you eat and drink during the chosen day
- Be as precise as possible when recording the types of foods you are eating (i.e. percentage of fat in your milk, salted or unsalted nuts, etc.)
- Remember to indicate the quantities, trying to be as precise as possible (i.e. 1 apple the size of a fist, 1 cup of raisin bran cereal, 1 cube of cheese 3c x 3cm)
- Also, indicate how the food is cooked (i.e. roasted, sauteed with oil, baked)
- It is best to complete the journal when you eat to assure the most accurate representation of your diet

Recording what you eat in your food diary



Pre-habilitation Program
FOOD DIARY

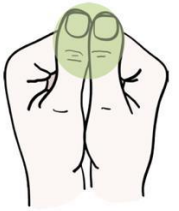
Patient Name: S. Connery

	Time	Place	Quantity	Food
Breakfast	8:00	home (kitchen)	1 cup 1 cup 1 (medium) 1.5 1 tbsp 2 tsp	bran flakes 2% milk banana filter coffee 10% cream sugar
Snack AM	10:00	home	125g 1 cup	Yoplait cherry yogurt earl grey tea
Lunch	noon	home	2 slices 1 slice 1 leaf 1 (medium-size of fist)	whole wheat bread Kraft SIngles cheese Romaine Lettuce apple
Snack PM				
Supper	7:00	home	1 cup 1/2 cup 1 tbsp 2 cups 5oz	whole wheat penne tomato basil sauce (Classico) olive oil water red wine
Snack (evening)			1 (palm sized)	oatmeal cookie

Learning Serving Sizes

Your hands can help you with portion sizes. The best way to find out how much food you are eating, or your portion size, is to use measuring cups, spoons or a scale. You can use your hands to help you determine how much you are eating when you don't have access to them.

2 Thumbs = 1 tablespoon



Peanut Butter
Salad Dressing
Sour Cream Dips

Palm of Hand = 3 – 4 ounces

Chicken
Cooked Meats
Fish

1 Hand = 1⁄2 Cup

Pasta, Rice
Hot Cereal (oatmeal) Beans
Mashed Potatoes Cottage
Cheese

2 Hands = 1 Cup

Soup
Green Salads
Mixed Dishes (Chili, Stew)

1 Fist = 8 fluid ounces

Cold and Hot Drinks

The Plate Method: This is a guide to help you naturally meet your daily nutrient needs and maintain portion control. Your lunch and dinner plate should look like this:

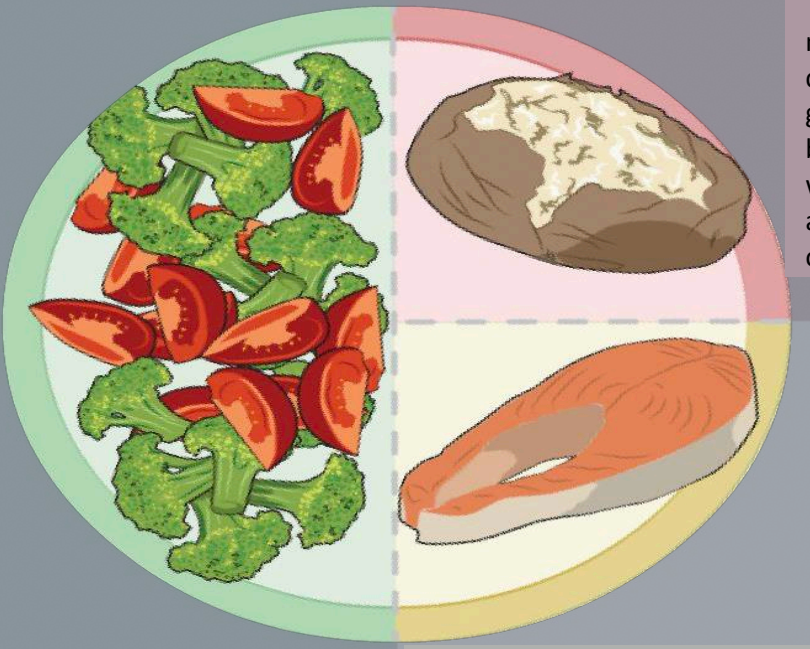
Non-Starchy Vegetables
Yellow or green beans, broccoli, brussels sprouts, cabbage, cauliflower, celery, kale, cucumber, eggplant, palm hearts, endive, leeks, lettuce, spinach, mushrooms, okra, onion, peppers, radish, tomatoes, zucchini.

Tip: Try salad, vegetable soup, stir fry, boiled or steamed vegetables.

Milk and Other Choices
Milk, fortified soy drinks, yogurt, kefir, cheese, no salt added cottage cheese.
Tip: Aim for 1%. These foods do not need to be present at each meal but are also a good source of protein, calcium and vitamin D.

Starch
Pasta, rice, quinoa, couscous, bread, pita, bread, cereal, oats, potato, peas.

Tip: Make majority of your choices whole grain. Choose barley, brown or wild rice, oats, and quinoa more often.



Fats
Favor vegetable oils. Use small amounts. Other fats can be added to a meal such as avocados

Fruits
Try fresh or frozen fruit that are bright in colour and limit fruit juices.
Goal: 2 -3 servings/day

Proteins
Eggs, fish, seafood, meat, poultry, nuts, nut butters, seeds, soy products such as tofu, beans, lentils, chickpeas, protein powder, meal supplements.
Tip: Choose lean meats, trim fat and remove skins from animal products before cooking. Try natural peanut butter without added sugar or salt. Choose beans, lentils and fish often. Try to always prioritize the protein on your plate.

Exercise Program

During your first study visit with the kinesiologist (an exercise specialist), they will help develop the right physical activity program for you. You will be shown how to performyour exercise program that will consist of 3 components: **strength training (also called resistance exercises), aerobic, and flexibility.**

- **Duration of Each Session:** Approximately 1 hour
- **Frequency:** as per schedule above

Questions about Strength Training

Why do we perform strength training?

Strength training helps to develop muscular strength. As your muscles become stronger, performing chores and activities of daily living should become easier.

Where can the exercises be performed and with what equipment?

Exercises will be performed at the Preoperative Program Centre as per the schedule above. Depending on your strength, other equipment such as an elastic band or weights might be suggested to you by the kinesiologist.

What if I forget my exercises?

All exercises are included in this pamphlet with pictures and cues. Please refer to **the Exercise Prescription** Section for your personalized program.

Questions about Aerobic Training

What is aerobic training?

Aerobic training consists of performing an activity such as walking, cycling, or swimming for a period of time at a prescribed intensity. The kinesiologist will prescribean appropriate duration and intensity that will be beneficial for you. While at the Preoperative Program Centre, you will train on an ergonomic stationary bike.

How do I know if I am working at the right intensity?

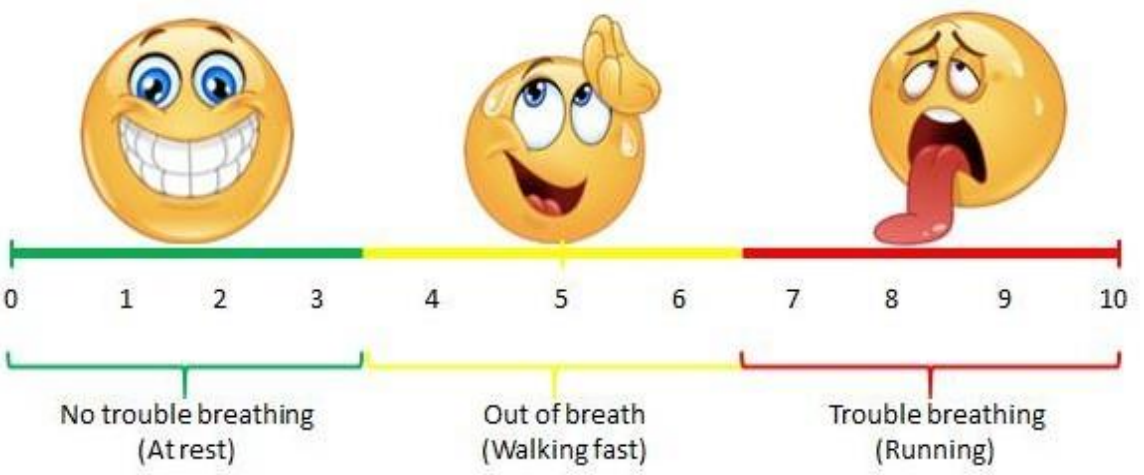
The kinesiologist will monitor you during the sessions to make sure you are achieving the targets set out with them. These targets are based on your age and fitness. We will also instruct you to record any other physical activity outside of the program in the "log" section using the **Borg scale** (a scale that rates how hard you feel that you are working).

The Borg Scale

The Borg Scale measures how hard you feel that you are exercising.

After your exercise, identify which number corresponds to how hard you worked throughoutyour training. A number 6 represents **very, very easy** exertion while number 10 signifies a **very very hard** effort.

Use these cues to help determine how hard you worked.



Resistance Exercises

☐ Shoulders

Instruction: Place your arms to your side and then raise your arm to theside so that your arm is now parallel to the floor. Do 1 set with 10 repetitions.

Reminder: Keep a small bend in your elbow throughout the movement. Perform the exercise one arm at a time.

☐ Biceps Curls

Instruction: Keeping your elbows attached to your sides, bend your elbows. Do 1 set with 10 repetitions.

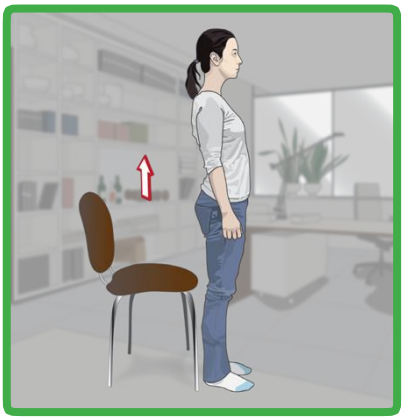
Reminder: Try to keep your back straight. Keep your wrists in line with your forearm.

☐ Triceps Extensions

Instruction: Hold one hand at your chest. Open your elbow so that your hand is behind your back. Do 1 set with 10 repetitions.

Reminder: Keep the elbow of the moving arm glued to your body during the entire movement.

☐ Quadriceps (Chair Squats)



Instruction: Sit at the edge of the chair with your legs at an angle of 90 degrees. Stand up without using your hands. Do 1 set with 10 repetitions.

Reminder: Always keep your legs at an angle of 90 degrees. The feet should not move at the beginning of the movement.

☐ Hamstring Curls

Instruction: Hold the back of a chair. Kick your heels back one at a time. Do 1 set with 10 repetitions.

Reminder: Do not put all of your body weight on the chair but on the standing leg instead. Keep your knees close together.

☐ Standing Calf Raises

Instruction: Stand facing the wall and hold for support. Lift your heels at the same time so that you are standing on your toes. Do 1 set with 10 repetitions.

Reminder: Keep your body straight (perpendicular to the floor).

Flexibility Exercises

Repeat 3 times per exercise.
Hold the position for at least 20 seconds

☐

Shoulders

Instruction: Keep hands at shoulder height.

Reminder: Try to keep your back straight.

☐

Biceps

Instruction: Extend one arm with the palm of your hand facing upwards. With the other hand, push the fingers backwards

Reminder: Keep your arm at shoulder height.

☐

Triceps

Instruction: Raise your arm up, and bend your elbow so that your hand is now touching between your shoulder blades. With the opposite hand, slightly pull your elbow to the opposite side.

Reminder: Do one arm at a time.

☐

Quadriceps

Instruction: Place one leg onto a chair behind you while holding on to an object in front of you for support.

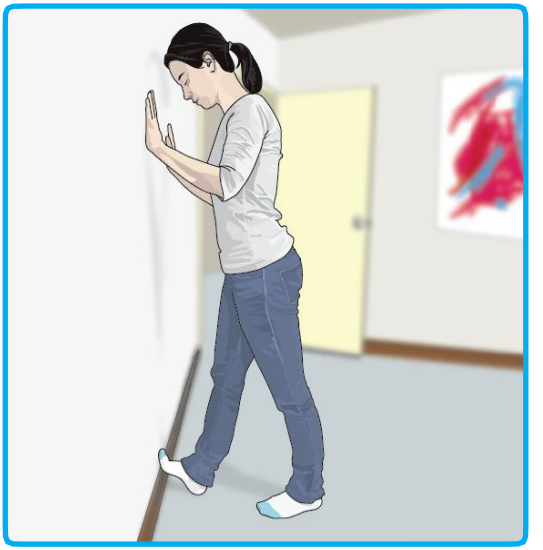
Reminder: Make sure to place your leg as far back as you can on the chair.

☐

Hamstrings

Instruction: Sit at the end of a chair with one leg fully extended. Place the heel of your foot on the floor and lean forward.

Reminder: Go as far as you can without feeling pain.



☐

Lower leg

Instruction: Stand with your hands against a wall. Place the toes of one of your feet on the wall in front of you and slightly push.

Reminder: Only do one foot at atime.

Journal
(before surgery)

Aerobic Training Journal: Example

Below is an example of how to fill out your training journal. Meet Ms. Anna Tremblay.

On **Sept. 2nd, 2020**, Ms. Tremblay met with the physiotherapist/ kinesiologist and was prescribed to walk **(W)** or bike **(B)** for **20 minutes, 3 times per week.**

It was recommended that she take 1 packet of protein po **before / after** resistance training.

It was recommended that she work at **50%** of her **Heart Rate Reserve** (a value calculated by the kinesiologist), and to aim for a **Target Heart Rate of 118 Beats per minute.** It was recommended that she walk 5000 steps three times per week.

Please see her prescription in the box at the bottom of the page**.**

	SUN	MON	TUES	WED	THUR	FRI	SAT
Resting Heart Rate		85		80		82	
Type of Exercise		W		B		W	
Duration		20 min		20 min		20 min	
Exercise Heart Rate		118		118		118	
Perceived Effort (BORG scale)		6		6		6	
Post Exercise Heart Rate		115		115		115	
Fitbit tracker: number of steps		5650		6760		8450	

Dates Sept 5 to Sept 12
Target Heart Rate: 118
% of Heart Rate Reserve: 50%

Duration: 20 min
Frequency: 3 times / week
Number of Steps: 5000

Aerobic Training

- Remember to take your heart rate before, during, and after your aerobic exercise
- Target Heart Rate is the heart rate at which you should aim to be working duringyour aerobic activity.
- For aerobic exercise, you can choose an activity that you like. In your exercise journal, indicate which activity you did by writing the first letter of that activity.
- During your exercise, you will rate your exertion level in your exercise

Resistance Training Journal: Example

	SUN	MON	TUES	WED	THURS	FRI	SAT
Nutrition - Protein Powder	✓		✓		✓		

Exercises	p.	sets	reps	sets	reps	sets	reps	sets	reps	sets	reps	sets	reps	sets	reps
Shoulders	17	1	12			1	12			1	12				
Biceps Curls	18	1	10			1	10			1	10				
Triceps Curls	18	1	10			1	10			1	10				
Quadriceps (Chair Squats)	19	1	12			1	12			1	12				
Hamstring Curls	20	1	10			1	10			1	10				
Standing Calf Raises	20	1	10			1	10			1	10				

Flexibility		SUN	MON	TUES	WED	THURS	FRI	SAT
Shoulders	22	✓		✓		✓		
Biceps	22	✓		✓		✓		
Triceps	23	✓		✓		✓		
Quadriceps	23							
Hamstrings	24	✓		✓		✓		
Lower leg	24	✓		✓		✓		

Nutrition - Protein Powder	✓		✓		✓		

Resistance Training

- Remember to record the number of repetitions and sets you performed for each strength training exercise.
- Remember to breathe throughout the entire exercise (breathe out when you push,and breathe in when you are not exerting force).

Aerobic Training

	SUN	MON	TUES	WED	THUR	FRI	SAT
Resting Heart Rate							
Type of Exercise							
Duration							
Exercise Heart Rate							
Perceived Effort (BORG scale)							
Post Exercise Heart Rate							

Dates_____to_____
Target Heart Rate: _____
% of Heart Rate Reserve: _____

Duration:_____
Frequency:_____
Number of Steps: _____

Notes:

Resistance Training

	SUN	MON	TUES	WED	THURS	FRI	SAT
Nutrition - Protein Powder							

Exercises	p.	sets	reps	sets	reps	sets	reps	sets	reps	sets	reps	sets	reps	sets	reps
Shoulders	17														
Biceps Curls	18														
Triceps Curls	18														
Quadriceps (Chair Squats)	19														
Hamstring Curls	20														
Standing Calf Raises	20														

Flexibility		SUN	MON	TUES	WED	THURS	FRI	SAT
Shoulders	22							
Biceps	22							
Triceps	23							
Quads	23							
Hamstrings	24							
Lower leg	24							

Nutrition - Protein Powder								

Notes:

Food diary

	Time	Location	Quantity	Food
Breakfast				
Snack				
Lunch				
Snack				
Supper				
Snack				

Notes

List of instructions for Prehab study in patients with cirrhosis undergoing liver transplantation

APPENDIX 2

Dry weight estimation

Instructions[1,2,3]:

- Measure participant weight
- Determine degree of ascites and bilateral pedal edema
- Subtract the following percentages from the measured weight:
    - 5% in case of mild ascites
    - 10% in case of moderate ascites
    - 15% in case of severe ascites
    - An additional 5% if bilateral pedal edema is present
- Record the wet weight, the degree of ascites and pedal edema, and the calculated dry weight
- The calculated dry weight will be used to calculated the BMI

Mid-Arm Circumference

Instructions:

- With the participant standing, place the non-dominant arm elbow flexed at 90* with the palm facing upwards
- Standing behind the participant, mark the midpoint between the lateral tip of the acromion and the most distal point on the olecranon process on the back of the arm
- With the non-dominant arm hanging freely, warp a flexible measuring tape around the midpoint of the upper arm identified above without applying excessive pressure and record the mid-arm circumference
- Repeat measurement twice for consistency and take the average

Triceps Skin Fold

Instructions:

- At the non-dominant mid upper arm point identified above, ensure the arm is hanging freeling,
- With your thumb and forefinger, pull a skinfold out in the vertical plane of about 2cm
- With your other hand holding a caliper, place the caliper jaws about 1cm in the vertical plane with the marked point in the center of the caliper jaws.
- Once the caliper is in place, release your thumb and forefing
- The length of the caliper opening will provide the tricep skin fold measurement
- Repeat measurement twice for consistency and take the average

Royal Free Hospital Global Assessment

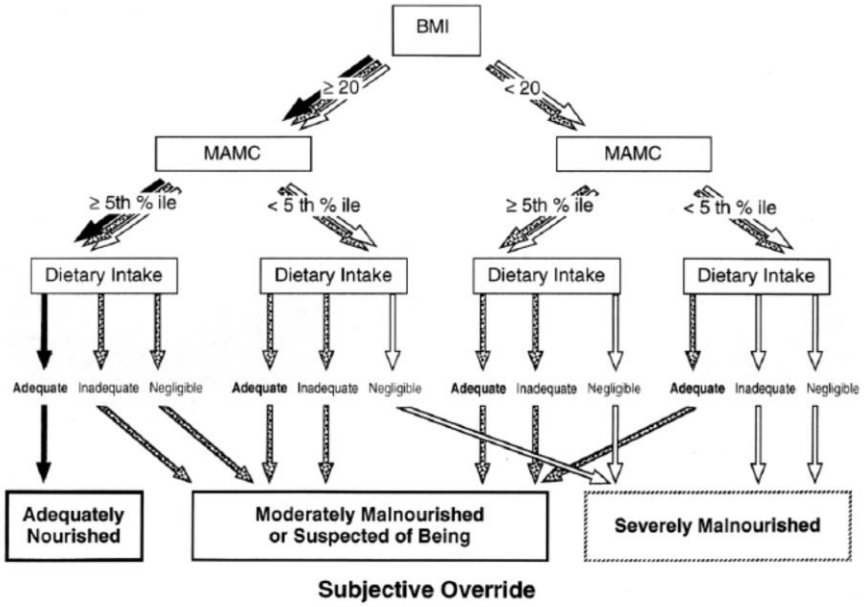
Instructions[4]:

1. Estimate dry weight as per above and calculate BMI
2. Measure the mid-arm circumference and the triceps skin fold thickness on the non-dominant side using a measuring tape and skinfold calipers
3. Calculate the mid-arm muscle circumference : MAMC = MAC – (TSF x 0.3142)
4. Convert MAMC into a percentile base on published standards (see table attached)
5. Estimate the dietary intake and classify as adequate, inadequate or negligible:
    - Adequate: meets estimated daily requirements
    - Inadequate: fails to meet requirements but exceeds 500kcal/day
    - Negligible: if provides less than 500kcal/day

Scoring:

1. Classify patients as per figure below as adequately nourished, moderately malnourished or severely malnourished allowing for a subjective override of no more than 1 contiguous category.

Supplementary Figure 1. Royal Free Hospital Subjective Global Assessment (RFH-SGA)



Standardized MAMC tables for men and women stratified by age[5] :

Age- and sex-specific reference values for the mid-upper arm muscle circumference of American men*

Age group	Sample size	Estimated population	Mean	Percentile						
				5th	10th	25th	50th	75th	90th	95th
yr		*millions*	*cm*							
18–74	5261	61.18	28.0	23.8†	24.8	26.3	27.9	29.6	31.4	32.5
18–24	773	11.78	27.4	23.5	24.4	25.8	27.2	28.9	30.8	32.3
25–34	804	13.00	28.3	24.2	25.3	26.5	28.0	30.0	31.7	32.9
35–44	664	10.68	28.8	25.0	25.6	27.1	28.7	30.3	32.1	33.0
45–54	765	11.15	28.2	24.0	24.9	26.5	28.1	29.8	31.5	32.6
55–64	598	9.07	27.8	22.8	24.4	26.2	27.9	29.6	31.0	31.8
65–74	1657	5.50	26.8	22.5	23.7	25.3	26.9	28.5	29.9	30.7

* Developed from data collected during the HANES of 1971 to 1974.
† Values are in units of cm.

Age- and sex-specific reference values for the mid-upper arm muscle circumference of American women*

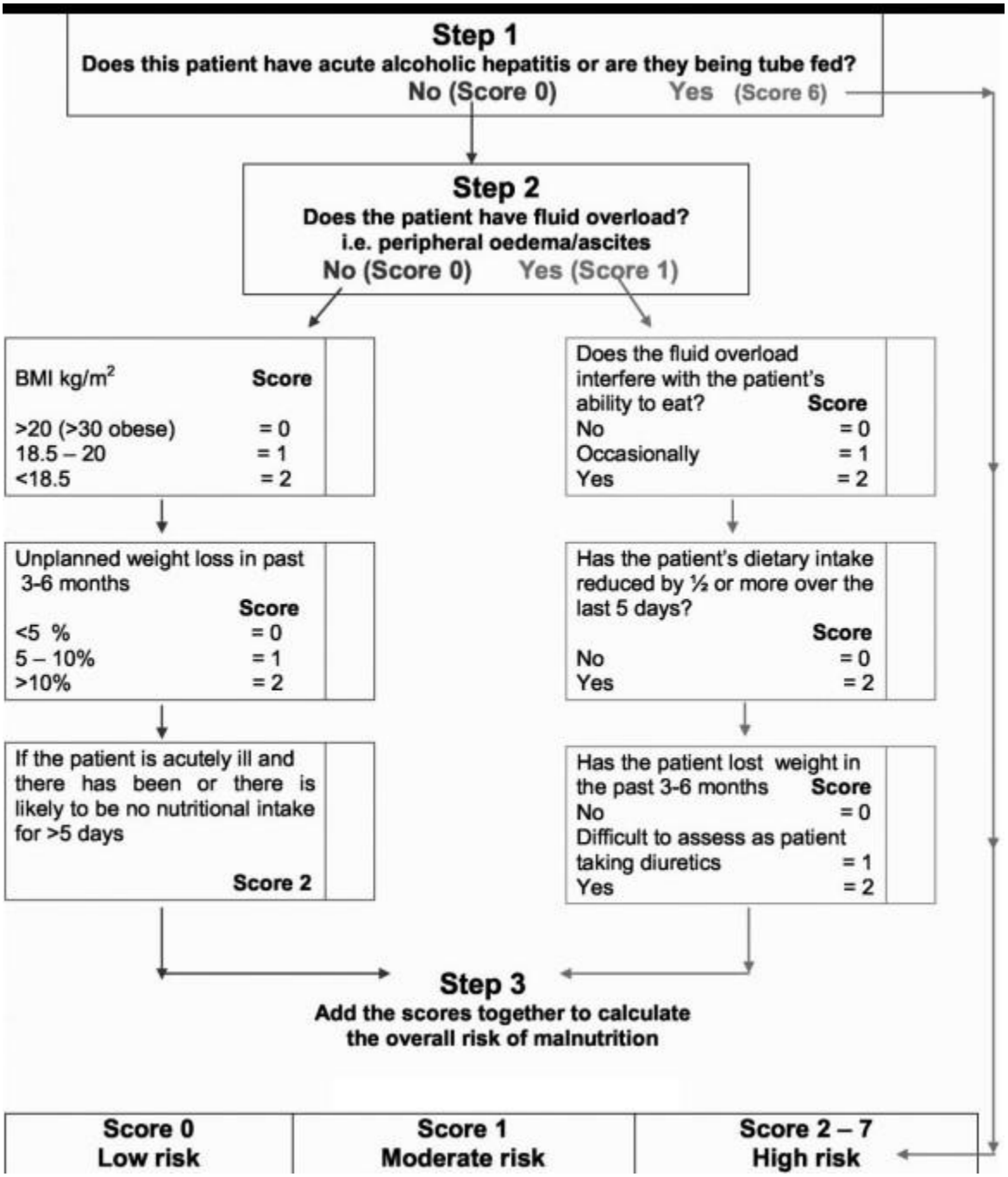
Age group	Sample size	Estimated population	Mean	Percentile						
				5th	10th	25th	50th	75th	90th	95th
yr		*millions*	*cm*							
18–74	8410	67.84	22.2	18.4†	19.0	20.2	21.8	23.6	25.8	27.4
18–24	1523	12.89	20.9	17.7	18.5	19.4	20.6	22.1	23.6	24.9
25–34	1896	13.93	21.7	18.3	18.9	20.0	21.4	22.9	24.9	26.6
35–44	1664	11.59	22.5	18.5	19.2	20.6	22.0	24.0	26.1	27.4
45–54	836	12.16	22.7	18.8	19.5	20.7	22.2	24.3	26.6	27.8
55–64	669	9.98	22.8	18.6	19.5	20.8	22.6	24.4	26.3	28.1
65–74	1822	7.28	22.8	18.6	19.5	20.8	22.5	24.4	26.5	28.1

* Developed from data collected during the HANES of 1971 to 1974.
† Values are in units of cm.

Royal Free Hospital Nutrition Prioritization Tool

Instructions[6]:

1. Follow the diagram below for step-wise assessment and scoring:

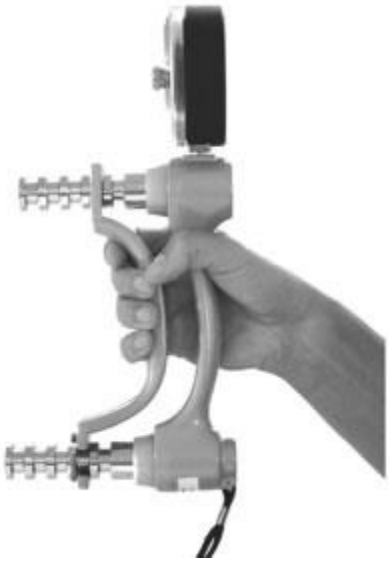


Liver Frailty Index

Instructions[7]:

1. Grip Strength
   - Set the adjustable handle to the standard position – second ring from the inside.
   - Have the patient use their **dominant** hand to grip the dynamometer. The patient should have a neutral shoulder and forearm, elbow at 90°, and not rest the device on anything during the test.
   - ***You say: "Please squeeze with your maximum strength and hold steadily for a few seconds".***

   Scoring of grip strength
   - Record the highest force exerted to the nearest kg. The red peak-hold needle will automatically remain at the highest force exerted.
   - Repeat this test three times. Reset the peak-hold needle to zero after each attempt.
   - Record all 3 attempts and calculate average.



2. Chair Stands
   - ***You say: "I would now like you to try to move your body in different movements. I will first describe and show each movement to you. Then I'd like you to try to do it. If you cannot do a particular movement, or if you feel it would be unsafe to try to do it, tell me and we'll move on to the next one. Let me emphasize that I do not want you to try to do any exercise that you feel might be unsafe".***
   - ***You say: "Do you think it would be safe for you to try to stand up from a chair five times without using your arms?"***
   - Have the patient sit in a chair with their feet touching the floor and arms crossed in front of their chest.
   - Instruct the patient that they must do five chair stands as fast as they can. Please demonstrate to the patient.
   - For each chair stand, the patient must stand up fully from the chair (with knees straight) and then sit down again as quickly as possible.

- ***You say: "Please stand up straight as QUICKLY as you can five times, without stopping in between. After standing up each time, sit down and then stand up again. Keep your arms folded across your chest. I'll be timing you with a stopwatch."***
- When the patient is properly seated, ***You say***: ***"Ready? Stand"*** and begin timing.
- Count out loud as the participant arises each time, up to five times.
- Stop if patient becomes tired or short of breath during repeated chair stands.
- Stop the stopwatch when he/she has straightened up completely for the fifth time.
- Also stop:
    - If the patient uses his/her arms
    - After 1 minute, if patient has not completed rises
    - At your discretion, if concerned for patient's safety
- If the patient stops and appears to be fatigued before completing the five stands, confirm this by asking ***"Can you continue?"***
- If the participant says "Yes," continue timing. If participant says "No," stop and reset the stopwatch.

Scoring of chair stands

- If the patient completed all 5 chair stands within 60 seconds, record the total time in seconds to one decimal place.
- If the patient did not complete all 5 chair stands in 60 seconds, enter 0 for the time.

3. Balance
    - Balance is tested in 3 positions – side-by-side, semi-tandem, and tandem (see picture below)-for 10 seconds each.
    - The tester may help the patient to get into the proper position, but they must hold the poses on their own without the assistance of a person, or a cane, walker, etc.
    - The patient can move their body during the testing to maintain balance but must keep their feet in the proper position.
    - If the patient cannot hold a pose for the full 10 seconds, allow them a second attempt. If still unable, record the time they held the pose in seconds to one decimal place.

    3.1 Side-by-Side

    - Demonstrate the side-by-side balance position.
    - ***You say: "I want you to try to stand with your feet together, side-by-side, for about 10 seconds. You may use your arms, bend your knees, or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop."***
    - Stand next to the patient to help him/her into the side-by-side position.
    - Supply just enough support to the patient's arm to prevent loss of balance.
    - When the patient has his/her feet together, ask ***"Are you ready?"***
    - Then let go and begin timing as you say, ***"Ready, begin."***
    - Stop the stopwatch and say ***"Stop"*** after 10 seconds or when the patient steps out of position or grabs your arm.

    Scoring of side-by-side

    - If the patient held the position for 10 seconds, record 10 seconds.
    - If the patient could not hold the position for 10 seconds, record the time to one decimal point.

3.2 Semi-Tandem

- Demonstrate the semi-tandem balance position.
- ***You say: "Now I want you to try to stand with the side of the heel of one foot touching the big toe of the other foot for about 10 seconds. You may put either foot in front, whichever is more comfortable for you. You may use your arms, bend your knees, or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop."***
- Stand next to the patient to help him/her into the semi-tandem position.
- Supply just enough support to the patient's arm to prevent loss of balance.
- When the patient has his/her feet together, ask ***"Ready, begin."***
- Stop the stopwatch and say ***"Stop"*** after 10 seconds or when the patient steps out of position or grabs your arm.

Scoring of semi-tandem

- If the patient held the position for 10 seconds, record 10 seconds.
- If the patient could not hold the position for 10 seconds, record the time to one decimal point.

3.3 Tandem

- Demonstrate the tandem balance position.
- ***You say: "Now I want you to try to stand with the heel of one foot in front of and touching the toes of the other foot for about 10 seconds. You may put either foot in front, whichever is more comfortable for you. You may use your arms, bend your knees, or move your body to maintain your balance, but try not to move your feet. Try to hold this position until I tell you to stop."***
- Stand next to the patient to help him/her into the tandem position.
- Supply just enough support to the patient's arm to prevent loss of balance.
- When the patient has his/her feet together, ask ***"Ready, begin."***
- Stop the stopwatch and say ***"Stop"*** after 10 seconds or when the patient steps out of position or grabs your arm.

Scoring of tandem

- If the patient held the position for 10 seconds, record 10 seconds.
- If the patient could not hold the position for 10 seconds, record the time to one decimal point.

Scoring:

To obtain Liver Frailty Index, enter above data on https://liverfrailtyindex.ucsf.edu/ and record result.

6-minute walking test

Suggested Equipment:

Borg scale

Pulse oximeter, heart rate monitor, blood pressure monitor

Stop watch or timer

Measured 30m walkway demarcated at both ends (or the distance used at the Prehab complex)

Chairs (number will depend on patient's condition and risk) with 2 placed at each end of walkway

Patient preparation:

1. Screen for contra-indications to 6MWT

2. Wear comfortable clothing.

3. Wear appropriate shoes for walking.

4. Wear corrective eyewear (if applicable).

5. Take their medications as usual.

6. Not have exercised vigorously within 2 hours of beginning the test.

Administering test:

1.Prior to walking say to patient: "The object of this test is to walk as FAR AS POSSIBLE for 6 minutes. You will walk back and forth along this course (demonstrate one lap) for six minutes. Do not run or jog. You may slow down if necessary. If you stop, I want you to continue to walk again as soon as possible. You will be informed of the time and encouraged each minute. Please do not talk during the test unless you have a problem or I ask you a question. You must let know if you have any chest pain or dizziness. When six minutes is up I will ask you to STOP where you are. Do you have any questions?".

2. To begin, position the patient at the starting point and say: Start now, or whenever you are ready (start stopwatch when walking starts).

3. During the test: Provide the following standard encouragements in even tones. Do not use other words of encouragement or body language to speed up.

- At 1 minute: You are doing well. You have 5 minutes to go.
- At 2nd minute: Keep up the good work. You have 4 minutes to go.
- At 3rd minute: You are doing well. You are halfway done.

- At 4th minute: Keep up the good work. You have only 2 minutes left.
- At 5th minute: You are doing well. You have only 1 minute to go.
- At 6th minute: Please stop where you are.

If the patient stops during the test: Allow the patient to rest or sit in a chair if they wish, and check SpO2 and heart rate. Ask the patient why they stopped. Keep the stopwatch running and advise: Please resume walking whenever you feel able.

4. At the end of the test: record the distance walked, the heart rate, blood pressure and rating of Perceived Exertion (RPE). The patient should remain in a clinical area for at least 15 minutes following an uncomplicated test.

Scoring:

Count the number of complete lengths walked, and the partial distance on the final length rounded to the nearest meter

Distance (meters) = (# lengths completed x walkway distance) + partial distance on final length

Record the total distance in meter

Chronic Liver Disease Questionnaire

Instructions[9]:

Short prompt for the patient:

This questionnaire is designed to find out how you have been feeling during the last two weeks. You will be asked about your symptoms related to your liver disease, how you have been affected in doing activities, and how your mood has been. It is made of 29 questions. Please complete all of the questions and circle only one answer for each question. This should take you 10 minutes.

Scoring:

A sub-score is calculated for each domain

The sub-score of a domain is calculated by taking the average score of that domain

The global score is calculated by adding the sub-score of each-domain and dividing by 6, with a low score indicating a lower health-related quality of life

Domains:

Abdominal symptoms: Items 1, 5, 17

Fatigue: Items 2, 4, 8, 11, 13

Systemic symptoms: Items 3, 6, 21, 23, 27

Activity: Items 7, 9, 14

Emotional function: Items 10, 12, 15, 16, 19, 20, 24, 26

Worry: Items 18, 22, 25, 28, 29

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