**Supplementary Material**

**Prehabilitation Exercise Prescription**

Patients were first evaluated by a liver transplant program-dedicated physical therapist (PT; P.M.B.) which included assessments of their range of motion, mobility, strength, and balance. Specific frailty metrics (dominant grip strength, 6-minute walk test, 4-meter gait speed test, 5x sit-to-stand) were also collected. Exercise prescriptions were modified based on the limitations found during each patient’s baseline evaluation, such as co-existing medical comorbidities (i.e., recent orthopedic surgeries, major fractures) or liver-related complications (i.e., bleeding esophageal varices). Supplementary Table 1 shows some real-life examples where adjustments to exercise prescription were made.

**Robust patients.** This group of patients were instructed to continue their current exercise regimen unless they specifically asked for a home exercise program (HEP). The HEP typically involved weights or resistance bands as well as aerobic components, such as treadmills, elliptical, or stationary bikes. Functional activities within the home were strongly encouraged.

**Pre-frail and frail patients.** This group of patients were given tailored HEP based on the deficits found during their baseline evaluation. Prehabilitation was provided online and on paper for convenience. Exercise recommendations were 150 minutes of activity per week, which breaks down to 30 minutes, five days a week.[1] The 30-minute workout could be broken down into smaller segments depending on exercise tolerance. The programs primarily targeted the major upper and lower body muscle groups with the use of weights and/or resistance bands. The incorporation of aerobic exercise was also recommended. Barriers to walking included cold temperatures, high fall risks, and the need for assisted devices. In such cases, the purchase of a restorator bike or pedal exerciser was recommended. Patients with hepatic encephalopathy were encouraged to use weights instead of exercise bands since they tend to be easier to perform. Additionally, caregivers were instructed on proper exercise techniques, to safely supervise patients with encephalopathy.

**Exercise strategies.** All patients were advised to begin by doing 10 repetitions of each exercise and to gradually increase by 5 to 10 repetitions until they felt that they were no longer being challenged. If weights were involved, they were advised to not increase the weight until they could complete 30 repetitions with ease. At that point, they were then advised to increase the weight by 1 lb, decrease the number of repetitions back to 10, and start the progression again. The same process was done with resistance bands. Most frail patients started with the lighter resistance bands, whereas most pre-frail patients used the higher resistance bands. Exercise safety was reviewed during each session. Patients were instructed to stop immediately if they experienced any symptoms and to inform their PCP if needed. Patients were taught proper breathing techniques, proper safety measures, avoiding Valsalva maneuver, and adequate hydration.

**Seated exercise program vs. standing exercise program.** The decision of whether a patient received a seated versus a standing exercise program was based on their baseline evaluation and frailty metrics. Patients with balance issues, joint pain, and those in the frail group were typically recommended a seated exercise program.

Example of a fully seated upper and lower body exercise program with weights included: biceps curls, chest press, shoulder abduction, shoulder extension, triceps extension, long arc quads, marches, hip abduction, hip adduction, and sit-to-stand (STS). Example of a fully seated program with resistance band included: shoulder front raise, biceps curls, shoulder extension, horizontal shoulder abduction, diagonal pulls in each direction, long arc quads, marches, hip abduction, hip adduction, and STS.

Example of a standing exercise program with weights included: biceps curls, shoulder flexion, shoulder abduction, chest press, triceps extension, mini squats, hip abduction, hip extension, marches, heel raises, and STS. Example of a standing exercise program with resistance bands included: biceps curls, shoulder abduction, shoulder extension, shoulder front raise/flexion, shoulder horizontal abduction, diagonal pulls both directions, mini squats (no band), hip flexion, hip extension, hip abduction, heel raises (no band), and STS.

As mentioned previously, the exercise programs were tailored to each individual patient and their limitations. Due to this, exercises were often interchanged between the programs listed above as deemed appropriate. At times, a completely different exercise may be implemented to address a particular deficit.

**Home health physical therapy vs. outpatient physical therapy.** Occasionally, patients were recommended home health physical therapy (HHPT) if they were very debilitated, did poorly during the baseline evaluation, or had difficulty arranging transportation. These patients often needed more guidance and supervision than HEP could provide. Similar patients with reliable transportation were recommended outpatient physical therapy, usually at a local clinic. Whether the patient was recommended HHPT or outpatient physical therapy, the patient was encouraged to give their treating PT permission to speak to the transplant clinic PT. This facilitated functional goal planning and assessment deemed necessary for transplant candidacy.

**Personal activity trackers and EL-FIT app:** Of note, in addition to the exercise programs described above, some patients were also issued personal activity trackers (PAT) for monitoring.[2] The data was transmitted to a secure database, where the PT could monitor step counts and advise the patients when needed. The patients were typically given a step count goal based on their functional status and their liver frailty index. As an example, the goal was typically 2500-4999 steps for a frail patient, 5000-7499 for pre-frail, and >7500 for robust. In addition to the PAT, few patients also had the option to sign up for EL-FIT, an exercise application designed by our group that can be accessed on any smartphone or tablet.[3] This application allowed patients to follow exercise videos. The videos were categorized based on baseline evaluation with an incremental increase in difficulty. Through the application’s dashboard, the staff can monitor how many videos the patients watched as well as the daily step counts recorded by the PAT.

**Follow-ups and adherence.** Once a month, the PT followed up with all the patients via phone calls. The patients were also given the PT’s contact information for any question or concerns that may arise during the training. At the follow-up prehabilitation visit (typically on the same day as their hepatology clinic visit), functional and frailty metrics were reassessed and compared to the previous visit’s. Follow-up pr visits also included evaluation of exercise adherence. Patients were asked how many days in an average week did they complete the HEP. Adherence of 4-5 days/week was considered “full” adherence and 1-3 days/week was considered “partial” adherence.[4] If they none were completed, they were considered “null” adherence. The HEP was then adjusted based on the patient’s progress or lack thereof, and this was recorded in the PT record in the EMR. If necessary, patients were recommended to attend formal outpatient or home health physical therapy. If adherence was an issue, the importance of increasing their participation in the exercise programs was again reviewed, and barriers to participation were addressed.

**References**

1. American College of Sports Medicine, et al., *ACSM's guidelines for exercise testing and prescription*. Tenth edition. ed. 2018, Philadelphia: Wolters Kluwer. 472 pages.

2. Dunn, M.A., et al., *Wearables, physical activity and exercise testing in liver disease.* Semin Liver Dis, 2020. **in press**.

3. Duarte-Rojo, A., et al., *Introducing EL-FIT (Exercise & Liver FITness), a smartphone app to prehabilitate and monitor liver transplant candidates.* Liver Transpl, 2020: p. in press.

4. Kruger, C., et al., *Home Exercise Training Improves Exercise Capacity in Cirrhosis Patients: Role of Exercise Adherence.* Sci Rep, 2018. **8**(1): p. 99.

**Supplementary Table 1.**

**Exercise prescription adjustment based on comorbidities and cirrhosis complications.**

|  |  |
| --- | --- |
| **Clinical Condition** | **Adjustment to Exercise Prescription** |
| Musculoskeletal concern  |  |
|  Low-back pain | Stretches added for area affected, low weights/low resistance; increased walking. If recent injury, recommend outpatient (OP) physical therapy PT for close monitoring and progress. |
|  Rotator cuff | Patient to try all exercises prescribed and call PT if problematic; weights/resistance to tolerance without exacerbation of symptoms and prescribed according to strength assessment during evaluation. If recent rotator cuff injury, referred to OP clinic for close monitoring and progression. |
|  Hip/knee pain | Possibly seated instead of standing exercises; usually holding mini squats as well as repeated STS exercise depending on the severity. Appropriate stretches added to target muscles affected. If recent injury, recommend OP PT for close monitoring and progress. |
| Cardiovascular disease | Self-pacing based on symptoms |
| At risk for hypoglycemia | Have a snack at hand |
| Hypotension | Patient started on midodrine along with exercise |
| At risk for falls | Chair - something to hold on toExercise with caregiver |
| Beta-blocker use | Avoid abrupt changes in positioning |
| Hepatopulmonary syndrome | Determined the need for supplementary oxygen while exercising |
| Fluid overload / refractory ascites | Self pacing depending on shortness of breath/symptoms; smaller increments of exercise done throughout the day; caution with standing exercises as balance may be affected (made sure patient had something to hold on to if standing exercises appropriate). Low weights/resistance |
| Esophageal/gastric varices Large being treated\* Small or status post-TIPS  Otherwise | NoneNoneRestrict weight lifting to 2-5 lbs; favor repetitions |
| Hepatic Encephalopathy | Exercise with caregiver |

TIPS: transjugular intrahepatic portosystemic shunt

\*Makes reference to primary / secondary prophylaxis with band ligation or use of beta-blocker

**Supplementary Table 2. Medical Comorbidities, CirCom Scores, and Frailty Metrics for 517 End Stage Liver Disease Patients**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Frailty by LFI** | **Frailty by 6MWT** | **Frailty by GST** |
|   | **Descriptor** | **Yes** | **No** | **p** | **Yes** | **No** | **p** | **Yes** | **No** | **p** |
| **Medical** **Comorbidities** |
| Obesity | 246 (49%) | 64 (55%) | 180 (47%) | 0.138 | 74 (60%) | 165 (45%) | 0.003 | 77 (63%) | 169(44%) | <0.001 |
| Any Active Cancer | 100 (20%) | 11 (9%) | 89 (23%) | 0.001 | 10 (8%) | 87 (23%) | <0.001 | 12 (9%) | 88 (23%) | 0.001 |
| Coronary Artery Disease  | 57 (11%) | 17 (14%) | 40 (10%) | 0.285 | 13 (10%) | 40 (11%) | 0.877 | 18 (14%) | 39 (10%) | 0.235 |
| Heart Failure | 24 (5%) | 13 (11%) | 11 (3%) | <0.001 | 11 (9%) | 10 (3%) | 0.004 | 14 (11%) | 10 (3%) | <0.001 |
| Peripheral Vascular Disease | 8 (2%) | 1 (1%) | 7 (2%) | 0.439 | 2 (1%) | 6 (2%) | 0.979 | 3 (2%) | 5 (1%) | 0.417 |
| Hypertension | 255 (50%) | 69 (56%) | 184 (48%) | 0.098 | 70 (55%) | 176 (47%) | 0.122 | 77 (60%) | 178(47%) | 0.009 |
| Type 2 DM | 227 (44%) | 66 (54%) | 159 (41%) | 0.014 | 67 (53%) | 154 (41%) | 0.025 | 74 (58%) | 153(40%) | 0.001 |
| CKD | 73 (14%) | 37 (30%) | 36 (9%) | <0.001 | 31 (24%) | 39 (11%) | <0.001 | 32 (25%) | 41 (11%) | <0.001 |
| Hemodialysis | 14 (3%) | 8 (7%) | 6 (2%) | 0.003 | 4 (3%) | 8 (2%) | 0.523 | 6 (5%) | 8 (2%) | 0.121 |
| COPD | 36 (7%) | 11 (9%) | 25 (6%) | 0.349 | 9 (7%) | 23 (6%) | 0.714 | 11 (9%) | 25 (7%) | 0.438 |
| Epilepsy | 11 (2%) | 3 (2%) | 8 (2%) | 0.805 | 3 (2%) | 8 (2%) | 0.885 | 5 (4%) | 6 (2%) | 0.117 |
| ActiveSubstance Use | 16 (3%) | 3 (3%) | 13 (3%) | 0.613 | 4 (3%) | 12 (3%) | 0.989 | 4 (3%) | 12 (3%) | 0.993 |
| All Beta-Blockers | 250 (49%) | 75 (61%) | 175 (45%) | 0.002 | 71 (55%) | 172 (46%) | 0.057 | 78 (61%) | 172(45%) | 0.002 |
| AnyAnticoagulation | 30 (6%) | 9 (7%) | 21 (6%) | 0.450 | 10 (8%) | 19 (5%) | 0.256 | 8 (6%) | 22 (6%) | 0.859 |
| **CirCom Scores** |
| CirCom 0 | 283 (55%) | 64 (51%) | 216 (56%) | 0.203 | 72 (56%) | 208 (56%) | 0.500 | 66 (50%) | 217(56%) | 0.250 |
| CirCom 1 | 54 (11%) | 10 (8%) | 44 (11%) | 12 (9%) | 40 (11%) | 15 (12%) | 39 (10%) |
| CirCom 1+1 | 8 (2%) | 4 (3%) | 4 (1%) | 4 (3%) | 3 (1%) | 5 (4%) | 3 (1%) |
| CirCom 3 | 150 (29%) | 42 (34%) | 108 (28%) | 34 (26%) | 110 (29%) | 40 (31%) | 110(29%) |
| CircCm 3+1 | 14 (3%) | 5 (4%) | 9 (2%) | 5 (4%) | 8 (2%) | 4 (3%) | 10 (3%) |
| CirCom 5 | 4 (1%) | 0 (0%) | 4 (1%) | 1 (1%) | 3 (1%) | 1 (1%) | 3 (1%) |
| CirCom 5+1 | 3 (1%) | 0 (0%) | 3 (1%) | 1 (1%) | 2 (1%) | 0 (0%) | 3(1%) |
| **Frailty Metrics** |
| LFI | 3.8(3.3-4.5) | 5.1(4.8-5.5) | 3.5(3.1-3.9) | <0.001 | 4.9(4.3-5.4) | 3.5(3.1-3.9) | <0.001 | 4.9(4.3-5.4) | 3.5(3.1-4.0) | <0.001 |
| 6MWT (m) | 326(244-390) | 168(95-251) | 360(294-411) | 156(83-209) | 363(307-415) | 168(96-226) | 360(301-412) |
| GST (m/s) | 1.0(0.8-1.2) | 0.7(0.5-0.9) | 1.1(0.9-1.3) | 0.7(0.5-0.8) | 1.0(1.1-1.3) | 0.7(0.5-0.8) | 1.1(1.0-1.3) |

6MWT, six-minute walk test; CirCom, cirrhosis comorbidities scoring system; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; GST, gait speed test; LFI, liver frailty index.

**Supplementary Table 3.**

**Final multivariable models showing clinical factor’s impact on each frailty metric.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **LFI** | **6MWT** | **GST** |
|  | **** | **p** | **** | **p** | **** | **p** |
| Age (years) | 0.021 | <0.001 | -2.46 | <0.001 | -0.004 | <0.001 |
| Sex (male) | -0.227 | 0.002 | 58.09 | <0.001 | 0.103 | <0.001 |
| BMI | --- | --- | -2.48 | 0.001 | -0.003 | 0.02 |
| NAFLD-ALD | 0.181 | 0.02 | -15.94 | 0.14 | --- | --- |
| HCC | 0.221 | 0.09 | --- | --- | --- | --- |
| Hemoglobin | -0.055 | 0.002 | 8.39 | 0.001 | 0.012 | 0.03 |
| Albumin | -0.341 | <0.001 | 50.02 | <0.001 | 0.110 | <0.001 |
| Large volume paracentesis | 0.175 | 0.02 | -25.01 | 0.01 | -0.096 | <0.001 |
| Active cancer | -0.312 | 0.02 | 21.09 | 0.106 | 0.075 | 0.02 |
| Heart failure | 0.539 | 0.02 | -96.01 | <0.001 | -0.280 | <0.001 |
| Hypertension | 0.120 | 0.11 | --- | --- | -0.062 | 0.01 |
| CKD | 0.304 | 0.004 | --- | --- | --- | --- |
| COPD | 0.301 | 0.02 | -44.31 | 0.02 | -0.099 | 0.03 |

6MWT, six-minute walk test; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GST, gait speed test; HCC, hepatocellular carcinoma; LFI, liver frailty index; NAFLD-ALD, non-alcoholic fatty liver disease and alcohol-associated liver disease (combined).

**Supplementary Table 4.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **One visit to LT PT****(n=308)** | **Two visits to LT PT (n=104)** | **Three or more visits to LT PT****(n=105)** | **P** |
| Age | 58 ± 11 | 57 ± 11 | 60 ± 10 | 0.15 |
| Male sex | 189 (61%) | 56 (54%) | 59 (56%) | 0.33 |
| BMI | 30.5 ± 7.0 | 29.3 ± 5.9 | 30.8 ± 7.5 | 0.21 |
| Listed for LT | 164 (53%) | 72 (69%) | 69 (66%) | 0.004 |
| NAFLD | 92 (30%) | 38 (37%) | 40 (38%) | 0.20 |
| ALD | 83 (27%) | 31 (30%) | 28 (27%) | 0.83 |
| Hemoglobin | 12.0 ± 2.3 | 11.6 ± 2.5 | 11.2 ± 2.2 | 0.007 |
| Albumin | 3.5 ± 0.6 | 3.3 ± 0.7 | 3.3 ± 0.6 | 0.01 |
| MELD | 12.8 ± 6.3 | 13.7 ± 7.0 | 12.4 ± 5.3 | 0.28 |
| Varices | 190 (63%) | 70 (68%) | 80 (76%) | 0.03 |
| Variceal bleed | 49 (16%) | 23 (22%) | 23 (22%) | 0.23 |
| Ascites | 199 (65%) | 75 (72%) | 78 (74%) | 0.16 |
| Large volume paracentesis | 109 (36%) | 41 (39%) | 49 (47%) | 0.14 |
| Hepatic encephalopathy | 150 (49%) | 64 (62%) | 57 (54%) | 0.09 |
| HCC | 40 (13%) | 10 (10%) | 11 (10%) | 0.58 |
| Beta-blocker | 142 (47%) | 48 (46%) | 60 (57%) | 0.15 |
| CirCom ≥3 ± 0 | 109 (36%) | 28 (27%) | 34 (32%) | 0.27 |

Comparison of baseline characteristics according to degree of programmatic compliance.

ALD, alcohol-associated liver disease; BMI, body mass index; CirCom, cirrhosis comorbidities scoring system; LT, liver transplant; HCC, hepatocellular carcinoma; MELD, model for end stage liver disease; NAFLD, non-alcoholic fatty liver disease; PT, physical therapist.

**Supplementary Table 5.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Full Adherence****(n=146)** | **Partial Adherence (n=198)** | **No Adherence****(n=41)** | **P** |
| Age | 57 ± 13 | 61 ± 10 | 61 ± 9 | 0.06 |
| Male sex | 93 (64%) | 98 (49%) | 22 (54%) | 0.03 |
| BMI | 30 ± 8 | 32 ± 8 | 32 ± 7 | 0.14 |
| Listed for LT | 114 (78%) | 127 (64%) | 26 (63%) | 0.01 |
| NAFLD | 55 (38%) | 85 (42%) | 16 (39%) | 0.60 |
| ALD | 43 (29%) | 49 (25%) | 8 (20%) | 0.37 |
| Hemoglobin | 11.6 ± 2.3 | 10.8 ± 2.1 | 10.8 ± 2.2 | 0.003 |
| Albumin | 3.4 ± 0.6 | 3.1 ± 0.1 | 3.0 ± 0.7 | <0.001 |
| MELD | 12 ± 6 | 13 ± 6 | 14 ± 8 | 0.36 |
| Varices | 100 (36%) | 158 (78%) | 29 (71%) | 0.03 |
| Variceal bleed | 30 (21%) | 39 (20%) | 7 (17%) | 0.88 |
| Ascites | 95 (65%) | 155 (78%) | 32 (78%) | 0.01 |
| Large volume paracentesis | 64 (44%) | 98 (49%) | 19 (46%) | 0.58 |
| Hepatic encephalopathy | 77 (53%) | 130 (66%) | 21 (51%) | 0.03 |
| HCC | 16 (11%) | 18 (9%) | 2 (5%) | 0.48 |
| Beta-blocker | 31 (21%) | 30 (15%) | 9 (22%) | 0.28 |
| CirCom ≥3 + 0 | 46 (32%) | 67 (34%) | 8 (20%) | 0.19 |

Comparison of baseline characteristics according to degree of exercise adherence

ALD, alcohol-associated liver disease; BMI, body mass index; CirCom, cirrhosis comorbidities scoring system; LT, liver transplant; HCC, hepatocellular carcinoma; MELD, model for end stage liver disease; NAFLD, non-alcoholic fatty liver disease.