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Outcomes of Exercise Interventions in Patients With Advanced Liver Disease: A Systematic Review of Randomized Clinical Trials.

Taher Jamali

Taaj Raasikh

Gabriel Bustamante

Amy Sisson

Puneeta Tandon

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Taher Jamali, MD*[1], Taaj Raasikh, MD*[1], Gabriel Bustamante, MD[1], Amy Sisson, MS[2], Puneeta Tandon, MD[3], Andres Duarte-Rojo, MD[4] and Ruben Hernaez, MD[5,6,7]

INTRODUCTION: **Frailty and sarcopenia are common complications of advanced liver disease. Owing to associated morbidity/mortality, there have been targeted efforts to prevent and/or improve both by enrolling these patients in focused exercise programs. This review systematically analyzes the data of randomized clinical trials (RCTs) on anthropometric, physical fitness, quality-of-life, and safety outcomes of exercise interventions in patients with advanced liver disease.**

METHODS: **Two authors independently searched trials on PubMed and EMBASE from inception up to November 18, 2021. A third independent arbitrator adjudicated all disagreements. We qualitatively summarized these outcomes as follows: (i) muscular fitness (maximal inspiratory/expiratory pressures, muscle size, muscle strength, and bioimpedance testing), (ii) cardiorespiratory fitness (cardiopulmonary exercise testing and 6-minute walk distance), (iii) quality of life, and (iv) others (safety or frailty indices).**

RESULTS: **There were 11 RCTs (4 home-based interventions) with 358 participants. Interventions ranged from 8 to 14 weeks and included cycling, walking, resistance exercises, balance and coordination training, and respiratory exercises. All described outcomes compared preintervention with postintervention measurements. Nine studies showed statistically significant improvements in at least 1 physical fitness variable. Ten studies showed statistically significant improvements in at least 1 muscular fitness variable. Six studies showed statistically significant improvements in at least 1 quality-of-life variable. Attrition rates ranged from 5% to 36%, and adherence rates ranged very widely from 14% to 100%. Only 1 study reported frailty indices. Notably, no complications of portal hypertension were seen in intervention groups in the 9 studies that reported these data.**

DISCUSSION: **A review of 11 RCTs with 358 participants with advanced liver disease demonstrates that exercise interventions can have favorable outcomes on muscular/cardiorespiratory fitness and quality of life. Although attrition and adherence varied, these interventions seem to be safe in patients with cirrhosis and are well tolerated.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/C565

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INTRODUCTION

Frailty and sarcopenia are prevalent complications in patients with advanced liver disease and cirrhosis. Sarcopenia is defined as a loss of skeletal muscle mass or function (muscular fitness), and in advanced liver disease, it is multifactorial in etiology with a significant impact on morbidity and mortality. Numerous studies suggest that sarcopenia is found in anywhere from 30% to 70% of patients with cirrhosis (1–4). Patients with cirrhosis who also have sarcopenia are at higher risk of mortality from sepsis than cirrhotic patients without sarcopenia (4).

[1]Department of Medicine. Baylor College of Medicine, Houston, TX Center, Houston, Texas, USA; [2]Texas Medical Center Library, Houston, Texas, USA; [3]Division of Gastroenterology (Liver Unit), Department of Medicine, University of Alberta, Edmonton, Alberta, Canada; [4]Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois [5]Section of Gastroenterology. Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX Center, Houston, Texas, USA; [6]Section of Gastroenterology and Hepatology, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA; [7]Center for Innovations in Quality, Effectiveness and Safety (IQuESt), Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, USA. **Correspondence:** Ruben Hernaez, MD. E-mail: ruben.hernaez@bcm.edu.
*Taaj Raasikh and Taher Jamali contributed equally to this work.
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Treatment of sarcopenia and frailty in advanced liver disease has focused on a combination of positive lifestyle changes (i.e., increasing daily physical activity) and adequate nutrition. Maintaining adequate protein intake and supplementation with branched-chain amino acids and leucine has been shown to improve levels of serum albumin and potentially protect against malnutrition and protein breakdown (5,6). It is also critical to recognize and optimize nutrition in the subset of patients who have sarcopenic obesity because this phenotype can be associated with increased mortality (7,8).

Several studies have been published about the benefits of exercise interventions in patients with early stages of liver disease. However, although exercise is recommended as an intervention in recent guidelines, we lack a systematic analysis of exercise tolerance and benefit in patients with advanced fibrosis and cirrhosis. Accordingly, our study provides a comprehensive systematic review regarding the safety and efficacy of exercise interventions in patients with advanced liver disease.

METHODS

Data sources and searches

We selected eligible studies by searching the PubMed and EMBASE electronic databases using predetermined search engines (see Table 1, Supplementary Digital Content 1, http://links.lww.com/AJG/C565) from inception to November 18, 2021. Our primary goal was to assess muscular and cardiorespiratory fitness (CRF) or other metrics of physical performance, quality-of-life, and safety outcomes of exercise interventions in patients with advanced liver disease. Per the American College of Sports Medicine Health-Related Physical Fitness Manual, physical fitness comprises 5 components: body composition (or anthropometrics), muscular strength and endurance (both equal muscle fitness), flexibility, and cardiorespiratory fitness (CRF) (9).

Study selection

We conducted a systematic review following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (10). Two independent reviewers (T.J. and T.R.) selected studies that addressed anthropometric, muscle mass/strength, CRF, frailty, quality-of-life, and safety outcomes in patients with advanced liver disease (either histologically defined as fibrosis stage F3 or F4 with or without portal hypertension or clinically defined as cirrhosis based on laboratory and imaging evidence) following the inclusion and exclusion criteria (see Table 2, Supplementary Digital Content 1, http://links.lww.com/AJG/C565). A third reviewer resolved disagreements (R.H.).

Study outcomes, data extraction, synthesis, and quality assessment

For each study, we assessed baseline study participant characteristics as follows: number of participants in each study group, percentage of participants in each Child-Turcotte-Pugh (CTP) class, types and schedule of exercise interventions, attrition rate, adherence rate, and information on any other intervention supplementing exercise if applicable (i.e., nutrition and diet counseling). We defined attrition as the percentage of participants in the study group that did not complete the study. We described adherence as the percentage of participants in the study group that participated in the exercise intervention as recommended by each study's initial design. We particularly searched for studies that included exercise interventions that had been shown to affect physical fitness, reverse sarcopenia, and reverse frailty, which included aerobic training (i.e., cycling, jogging, and respiratory exercises), resistance training (i.e., resistance bands and weight lifting), and balance and strength training (i.e., sitting to standing exercises and leg raises). We excluded studies that did not include 1 of these types of interventions. We also excluded studies that did not prioritize the outcomes described below.

We qualitatively summarized the following outcomes: (i) muscular fitness (muscle size, muscle strength, respiratory muscle strength (maximal inspiratory pressure and maximal expiratory pressure), muscle/lean body/body cell mass, isometric grip strength, and bioimpedance testing), (ii) CRF (6-minute walk distance [6MWD], peak oxygen consumption [$_{peak}VO_2$], ventilatory anaerobic threshold time, ventilatory efficiency, forced expiratory flow 25%–75%, root mean square [RMS] of the diaphragm and functional capacity, and 2-minute step test), (iii) self-reported quality-of-life outcomes (Chronic Liver Disease Questionnaire [CLDQ] parameters, Short-Form 36-Item Survey [SF-36] parameters, Sickness Impact Profile parameters, and EuroQol visual analog scale [EQ-VAS] parameters), and (iv) others (safety or frailty indices including complications of cirrhosis from exercise interventions). The preintervention measurements were compared with the postintervention measurements for all outcomes described.

We provided qualitative data as reported in the studies for the baseline characteristics of the study participants as described above. We primarily focused on statistically significant changes in the intervention group compared with their reported baseline for outcome data. We defined statistical significance by a *P*-value of less than 0.05 and a 95% confidence interval. We also reported data on statistically significant differences between the intervention and control groups (if any). We decided not to pursue a meta-analysis because of the substantial heterogeneity of the studies in outcome data and baseline study characteristics. We instead provided a qualitative summary of the data collected. Ranges were reported from the lowest value to the highest value. Mean values were reported as an average of the values with a standard deviation.

We independently assessed the methodological quality of the articles using a modified revision of version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2), resulting in each study being classified in 1 of the following categories: high risk of bias, low risk of bias, or some concerns for bias (11). We analyzed 5 domains, including the risk of bias arising from the randomization process, risk of bias due to deviations from the intended intervention (effect of intervention assignment), risk of bias due to deviations from the intended intervention (effect of adherence to intervention), risk of bias due to missing outcome data, and risk of bias in the measurement of outcomes. The specific parameters that were addressed in each domain for each study are presented in Table 1.

RESULTS

Our search algorithm identified 11 randomized clinical trials (RCTs) with a total of 358 participants (see Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/C565). All the studies were published from the years 2014–2020. Six trials included on-site exercise interventions (12–17), 4 trials solely included home-based exercise interventions (18–21), and 1 trial had partially home-based exercise interventions (22). Prescribed exercises ranged from 8 to 14 weeks and included cycling,

Table 1. Risk of bias among studies[a]

First Author, year	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall risk of bias
Limongi, 2014	Low	Low	Moderate	Low	Moderate	Moderate
Román, 2014	Low	Low	Low	Low	Low	Low
Zenith, 2014	Low	Low	Moderate	Low	Moderate	Moderate
Limongi, 2016	Low	Moderate	Moderate	Low	Low	Moderate
Macias-Rodriguez, 2016	Low	Moderate	Low	Low	Low	Low
Román, 2016	Low	Low	Moderate	Low	Low	Low
Kruger, 2018	Low	Low	Moderate	Low	Low	Low
Wallen, 2019	Low	Low	Moderate	Low	Low	Low
Aamann, 2020	Low	Low	Moderate	Low	Low	Low
Chen, 2020	Low	High	Moderate	Low	Moderate	High
Lai, 2020	Moderate	Low	Moderate	Low	Low	Moderate

Domain 1: Risk of bias arising from the randomization process.
Domain 2: Risk of bias due to deviations from the intended intervention (effect of assignment to intervention).
Domain 3: Risk of bias due to deviations from the intended intervention (effect of adhering to intervention).
Domain 4: Risk of bias due to missing outcome data.
Domain 5: Risk of bias in measurement of outcomes.
[a]Analyzed using a modified version of the RoB2 tool (a revised Cochrane risk-of-bias tool for randomized trials).

walking, resistance exercises, balance and coordination training, and respiratory exercises.

Baseline characteristics of the participants

There were a total of 358 participants: 192 participants in the exercise groups and 166 participants in the control groups. The sample size for exercise groups ranged from 5 to 58 participants compared with 10–25 participants in the control group. The total sample size of the studies (including both exercise and control groups) ranged from 17 to 83 participants.

Nine studies reported CTP cirrhosis class data (12–14,16,17,22) and 2 did not (15,21). The CTP class for the studies varied significantly, with 1 study by Román et al. (12) reporting 100% of the participants with CTP class A cirrhosis. Another study by Chen et al. (20) reported 100% of the participants in classes B/C. The mean percentages of participants with reported CTP classes were 65% (SD 19) for class A and 37% (SD 21) for CTP classes B/C.

Type and schedule of exercise intervention and other interventions

The type of rehabilitation varied across the 11 studies and included aerobic exercises, resistance exercises, balance and coordination training, scheduled counseling/motivation, and personal activity trackers. The weekly schedules for each study varied from daily to a minimum of 3 times per week. The study duration ranged from 8 weeks to 12 weeks.

Eight studies included some form of aerobic exercise (6 studies with cycling [12,13,16–18,22], 2 studies with walking (12,17), and 2 studies with respiratory exercises (15,21)). Six studies included resistance and strength exercises, such as resistance bands or weight lifting (12,14,16,19,21,22). Three studies included some form of scheduled exercise counseling and/or motivation (19,20,22). Two studies included balance and coordination training in the exercise regimen (12,16). Finally, 2 studies included a personal activity tracker so that participants and study coordinators could follow activity levels (20,22).

Six studies supplemented dietary counseling and society guideline-based nutritional therapy in addition to physical rehabilitation (13–16,18,20). One study specifically added leucine supplementation (17).

Attrition and adherence rates

Adherence was measured by participation in the assigned exercises in each of the studies (in either supervised or unsupervised settings). Achieving specific intensities or duration of exercise was not necessarily delineated. One study did not include information about the adherence rate (15). Two studies did not include information about attrition and adherence rates (13,21). Of the remaining 8 studies that did include these data about intervention groups, attrition rates ranged from 5% to 36% and adherence rates ranged very widely from 14% to 100%. The mean attrition rate was 16% (SD 11), and the mean adherence rate was 77% (SD 27).

Outcomes

Muscular fitness. Overall, 10 of the 11 studies showed statistically significant improvements in at least 1 muscular fitness variable compared with participant baselines (12–18,20–22). Variation existed among the specific variables studied; however, many studies used computed tomography, magnetic resonance imaging, specific appendage measurements, bioelectrical impedance analysis, and dual energy X-ray absorptiometry (DEXA) to obtain anthropomorphic data. Only 1 study did not demonstrate any statistically significant change in any of the muscular fitness variables analyzed (19). Four studies showed statistically significant improvement in thigh circumference (12,13,17,18). Two studies showed statistically significant improvement in maximal inspiratory pressure (15,21). Other individual studies showed statistically significant improvements in muscle strength/size/dry lean mass (14), bioimpedance phase angle (16), body mass index (17), computed tomography-based psoas muscle index (20), maximal expiratory pressure (21), and isometric grip strength (22) (Table 2).

Cardiorespiratory fitness

Nine of the 11 studies showed statistically significant improvements in at least 1 CRF variable compared with participant baselines. Variables across studies were collected using cardiopulmonary exercise testing protocols, cycloergonomic testing, and 6MWD measurements. Two studies did not demonstrate any statistically significant change in any of the physical fitness variables analyzed (19, 22). Five studies showed statistically significant improvement in 6MWD (13,14,17,18,20). Three studies showed statistically significant improvements in $_{peak}VO_2$ and VE (13,16,18). Other individual studies showed statistically significant improvements in ventilatory anaerobic threshold time (12), forced expiratory flow 25%–75% (21), RMS of the diaphragm and functional capacity (15), and steps climbed in the 2-minute step test (17) as outlined in Table 2.

Specific 6MWD increases in meters were noted as follows: 423 ± 60 to 482 ± 87 (20); 509 ± 85 to 541 ± 100 (14); 503.6 ± 96.3 to 534.0 ± 102.7 (18); 529.1 ± 131.8 to 570.5 ± 112.0 (13); and 365 (160–420) to 445 (250–500) (17). $_{peak}VO_2$ measurements also increased in the exercise groups in 3 of the studies, measured in mL/kg/min (23.3 ± 7.7 to 27.3 ± 6.2 (13); 21.4 ± 0.8 to 23.0 ± 1.3 (12); and 18.5 ± 4.5 to 21.4 ± 6.7 (18)). Respectively, in these studies, 6MWD increased on average by 48.3 m and $_{peak}VO_2$ measurements increased on average by 2.83 mL/kg/min.

Quality of life

Six studies showed statistically significant improvements in at least 1 quality-of-life variable compared with participant baselines (13–17,21). One study did not report any quality-of-life outcome data (12). Five studies reported data using CLDQ (13,16,18,19,22), 2 studies using EQ-VAS (13,18), 4 studies using SF-36 (14,15,17,21), and 1 study using the Sickness Impact Profile (20). Two studies (13,16) reported a statistically significant improvement in 1 CLDQ parameter each (fatigue and worry). Four studies (14,15,17,21) reported a statistically significant improvement in at least 1 SF-36 parameter (vitality, mental health, general health, and social function), including 1 study that showed a statistically significant improvement in the overall SF-36 score (21). One study showed a statistically significant improvement in self-perceived health status from the EQ-VAS score (13). The remaining studies that did not report any statistically significant changes in quality-of-life scores overall or in the individual parameters are presented in Table 2.

Between group differences

We also examined any statistically significant differences in anthropometrics, muscular or CRF, and quality-of-life outcomes between the control groups and the intervention groups for each study. Five studies did not report any statistically significant difference between study groups (12,18,19,21,22). Of the remaining 6 studies, 4 studies showed a statistically significant improvement in muscular fitness variables (thigh circumference (13,17), muscle strength by knee extension peak torque (14), weight/body mass index (17), and computed tomography-based psoas muscle index [20]). Five studies showed a statistically significant improvement in CRF (6MWD (13,17,20), peakVO$_2$ (13), RMS of the diaphragm (15), VE/VCO$_2$ (16), and steps climbed during the 2-minute step test (17)). One study showed a statistically significant improvement in quality-of-life variables (subscores of the CLDQ (13)). (Table 2)

Frailty, complications of cirrhosis, and safety

Only 2 studies reported frailty indices (12,19). The study by Lai et al. (19) reviewed liver frailty index data and did show an improvement after interventions in each arm; however, it was not statistically significant. The study by Román et al. (12) reviewed data on the Timed Up and Go test—an estimate of fall risk—and they demonstrated a statistically significant improvement in the test after 12 weeks in the intervention group. Notably, no complications of cirrhosis, including decompensation events, were seen in any of the intervention groups in the 9 studies that reported these data. Another key finding in the study by Macias-Rodriguez et al. was that patients with elevated hepatic venous pressure gradient (HVPG) were included and were safely able to participate in exercise interventions. The study demonstrated a statistically significant improvement in HVPG that favored the exercise group (16).

Quality assessment of studies

For the 11 RCTs, the modified Cochrane risk-of-bias tool showed that most of the studies (6 of 11) were at low risk of bias (12,14,16–18,22). Only 1 study (20) showed high concern for bias. The remaining 4 studies only showed moderate concerns for bias (13,15,19,21). The primary domain across all studies that showed the highest concern for bias was domain 3, which analyzed the effect of adherence to intervention. There was also some concern for bias from the effect of deviation from the intended intervention and from the measurement of outcome data (Table 1).

DISCUSSION

Our review of 11 RCTs with 358 participants with advanced liver disease evaluating the outcomes of physical rehabilitation demonstrates 3 major findings. First, having these patients participate in exercise interventions demonstrated statistically significant improvements in muscular and CRF and quality-of-life variables. An improvement in sarcopenia measured by thigh circumference was the most common change in muscular fitness category (observed in 4 of 11 studies) (12,13,17,18). Regarding CRF, a statistically significant improvement in 6MWD in the exercise study group was seen in 5 of the 11 studies (13,14,17,18,20) and $_{peak}VO_2$ in 3 of the 11 studies. These 2 CRF variables have individually and directly been associated with improved survival in patients with cirrhosis (24,25). Pimentel et al. demonstrated that low 6MWD was an independent predictor of mortality ($P = 0.01$) (23). In addition, the study by Faustini Pereira et al. (24) showed that individuals who covered a 6MWD shorter than 410 m had a survival rate of 55% compared with a rate of 97% for the individuals who walked more than 410 m ($P = 0.0001$). This study also demonstrated that individuals with $_{peak}$VO2 values less than 17 mL/kg had a survival rate of 55% compared with a rate of 94% for those with values more than 17 mL/kg ($P = 0.0001$). Thus, the magnitude of improvement in these variables is more clinically significant because of associations with survival. In addition, 6 studies reported improvement in a quality-of-life variable (13–17,21). The lack of consensus among the studies could be explained by the varying outcomes analyzed and the different types of exercises performed by each study.

LIVER

Table 2. Summary of randomized clinical trials describing outcomes of exercise interventions for patients with advanced liver disease

First author, year	No. of participants in exercise group(n), control group(n)	% Child-Turcotte-Pugh class	Type and schedule of exercise intervention	Attrition % and adherence % of the exercise group	Muscular fitness outcomes[b]	Cardiorespiratory fitness outcomes[b]	Quality-of-life outcomes[b]
Limongi, 2014	5, 12	NR	Per patient preference for 12 wk [a]Respiratory, resistance, and abdominal exercises	NR	Improvement (1–2)	Improvement (10)	Improvement overall (SF-36)
Román, 2014	10, 10	81% A, 13% B, 6% C	3 d a week for 12 wk Cycling and walking	20%, 83.3%	Improvement (3, 4)	Improvement (11, 12)	Improvement in general health, vitality, and social function (SF-36)
Zenith, 2014	9, 10	74% A, 26% B	3 d/wk for 8 wk Cycling	NR	Improvement (3)	Improvement (11, 13)	Improvement in fatigue (CLDQ) and self-perceived health status (EQ-VAS)
Limongi, 2016	22, 23	NR	Daily for 12 wk Respiratory and abdominal exercises	36.3%, NR	Improvement (1)	Improvement (14)	Improvement in general and mental health (SF-36)
Macias-Rodriguez, 2016	14, 15	64% A, 36% B	3 d/wk for 14 wk Cycling, strength training, coordination, and balance	21.4%, 97%	Improvement (5)	Improvement (13)	Improvement in worry (CLDQ)
Román, 2016	15, 10	100% A	3 d/wk for 12 wk Cycling, walking, resistance exercise, coordination, and balance	6.67%, 93.61%	Improvement (3, 6)	Improvement (15)	NR
Kruger, 2018	20, 20	70% A, 30% B	3 d/wk for 8 wk [a]Cycling	5%, 55%	Improvement (3)	Improvement (11, 13)	No change (EQ-VAS and CLDQ)
Wallen, 2019	10, 11	38% A, 62% B/C	3 d/wk (2 supervised and 1 unsupervised) for 8 wk PAT, counseling, resistance exercises, cycling, and walking	10%, 95% (supervised), and 75% (unsupervised)	Improvement (7)	No change	No change (CLDQ)
Aamann, 2020	20, 19	50% A, 50% B	3 d/wk for 12 wk Strength training	5%, 81.9%	Improvement (8)	Improvement (11)	Improvement in vitality and mental health (SF-36)
Chen, 2020	9, 11	78% B, 22% C	Biweekly counseling, PAT per patient preference for 12 wk [a]PAT and counseling	11.1%, 100%	Improvement (9)	Improvement (11)	No change (SIP)
Lai, 2020	58, 25	46% A, 54% B/C	3 d/wk for 12 wk [a]Coaching, resistance exercise, and motivation	26%, 14%	No change	No change	No change (CLDQ)

1. Maximal inspiratory pressure; 2. Maximal expiratory pressure; 3. Thigh circumference; 4. Body mass index; 5. Bioimpedance phase angle; 6. Mid-arm circumference and skinfold thickness; 7. Isometric grip strength; 8. Muscle strength, size, and lean dry mass; 9. Psoas muscle index based on computed tomography; 10. Forced expiratory flow (25%–75%); 11. 6-minute walk distance; 12. Steps climbed in a 2-minute step test; 13. Peak oxygen consumption or ventilatory efficiency; 14. RMS of the diaphragm and functional capacity; 15. Ventilatory anaerobic threshold time.
CLDQ, Chronic Liver Disease Questionnaire; EQ-VAS, EuroQol visual analog scale; NR, not reported, PAT, physical activity tracker; SF-36, Short-Form 36-Item Survey; SIP, Sickness Impact Profile.
[a]Indicates home-based exercises.
[b]Statistically significant outcomes compared with preintervention baseline.

Secondly, 9 of the 11 studies reported no complications or decompensation of a patient's cirrhosis caused by physical activity, regardless of the CTP class. The other 2 studies did not comment on complications because this was not a primary outcome in most included studies. Another important finding from the study by Macias-Rodriguez et al. (16) was that patients with elevated HVPG could safely participate in exercise interventions and actually display improvement in HVPG after weeks of physical rehabilitation. Furthermore, a nonrandomized uncontrolled pilot study by Berzigotti et al. (25) showed a statistically significant improvement in HVPG after an intensive 16-week diet and exercise intervention. These findings suggest that for patients with advanced liver disease and high CTP scores, physical rehabilitation is safe and results in favorable improvements in factors that contribute to poor outcomes.

Thirdly, the attrition and adherence rates among participants varied across studies. Nine of the 11 studies reported complete data on attrition and adherence rates among participants of the exercise/intervention groups. The attrition rates ranged from 5% to 36% for the 9 studies that reported these data. The study by Ligmoni et al. had the highest attrition rate at 36% because 8 patients were excluded from the initial intervention group of 22 participants. Three patients declined to do the exercises, 3 died before starting the intervention, and 2 underwent liver transplantation. The study by Lai et al. from 2020 had the second highest attrition rate of 26%. Otherwise, attrition rates were relatively lower for the other studies. Concerning adherence, studies with home-based, mostly unsupervised exercises had adherence rates ranging from 14% to 100% among participants. Those who had supervision during physical exercises had an adherence rate between 81% and 100%. Overall, studies that had supervised physical activity sessions rather than home-based exercises tended to have a higher adherence rate (Table 2). The differences in supervised versus unsupervised interventions can also affect efficacy and outcomes of exercise interventions. For example, the between-group changes in $_{peak}VO_2$ in the intervention group compared with the control group was lower in the study by Kruger et al. (18) (a home-based exercise study) compared with the study by Zenith et al. (13) (a supervised exercise study). As discussed earlier, lower adherence in unsupervised studies can negatively affect exercise-related gains. However, these studies also acknowledge the difficulties with implementation of regular supervised programs, including barriers of transportation, patient costs, and time commitment.

Finally, our review demonstrates a potential for improvement in sarcopenia and frailty in patients with cirrhosis. Román et al. (12) showed a statistically significant improvement in risk of falls using the Timed Up and Go test, and another nonrandomized uncontrolled trial by Williams et al. (26) showed a statistically significant improvement in functional capacity using the short physical performance battery test after a 12-week home-based exercise program. The study by Lai et al. did show an improvement in liver frailty index (LFI); however, this was not statistically significant likely because of the relatively small sample size. The other 9 studies in our review of randomized trials did not evaluate frailty metrics. Thus, there is clearly a lack of connection between risk estimation (frailty) and interventions for risk reduction in cirrhosis because it seems that physical rehabilitation studies rarely test for frailty or its reversal.

The strength of our review is that we only evaluated RCTs, thereby trying to preserve the quality of the studies analyzed and attempting to minimize bias. Most studies demonstrated a low risk of bias, and only 1 study demonstrated a high risk of bias (20). Our review supports the growing evidence that rehabilitation in patients with cirrhosis is feasible and safe. An additional strength of our review is that we analyzed outcomes of verified quality-of-life questionnaires. To the best of our knowledge, the impact of rehabilitation on the quality of life of patients with cirrhosis have not been systematically reviewed previously. There were, however, a few notable limitations of this review. Because we had very strict inclusion and exclusion criteria, we were only able to isolate 11 RCTs leading to an overall low sample size of both studies and total patients. We were also unable to perform a meta-analysis on the collected data because of the heterogeneity of outcomes and types of exercise interventions across the studies. Finally, the highly variable attrition and adherence rates across the studies further complicate interpretation of the results, with low attrition and adherence rates in select studies potentially affecting outcomes.

Interestingly, 5 of the 11 studies analyzed did not demonstrate a statistically significant difference between control and intervention groups in their respective outcomes (12,18,19,21,22). We hypothesize 3 possible explanations for these absences of differences. First, there was a mean 10.53% attrition rate and a mean 53.92% adherence rate in participants of these 5 trials, which could have led to underestimation of measurable benefits. Second, the target population may have diluted the effect. For example, in the study by Lai et al., the authors commented that the exercise program was designed for frail and elderly patients and may not have been rigorous enough for nonelderly nonfrail subjects. Finally, the exercise interventions likely need to be combined with a nutritional intervention to show benefit. In 5 of the 6 studies that demonstrated a difference in respective outcomes between study groups, it was observed that nutritional interventions were included (13–17,20). This finding may suggest that sufficient calorie and protein intake may be necessary alongside exercise to enhance muscle anabolism and have a maximal effect on muscle function. Per 2021 AASLD practice guidelines by Lai et al. (27), the caloric needs of adults with cirrhosis should be personalized with indirect calorimetry, with limited data supporting a caloric intake of 35 kcal/kg body weight per day in nonobese patients and lower targets in obese patients with cirrhosis in the absence of calorimetry measurements. The recommended daily protein intake per these practice guidelines is 1.2–1.5 g/kg ideal body weight per day. In summary, the weight of the evidence suggests that adequate sample size, stratification by frailty, and adequate calorie and protein intake are needed to maximize the impact on outcomes.

Our review showed that most of the studies looked at the feasibility of exercise interventions in this population while also evaluating initial outcomes of physical rehabilitation on frailty and sarcopenia metrics. These initial results are promising that these interventions can be safe and feasible and can statistically improve certain parameters of frailty and sarcopenia. Given the negative consequences associated with frailty and sarcopenia and the findings of our systematic review, we would strongly support additional studies with larger sample sizes to evaluate primary outcomes such as the survival benefit of physical rehabilitation in patients with advanced liver disease.

CONFLICTS OF INTEREST

Guarantor of the article: Ruben Hernaez, MD, MPH, PhD.
Specific author contributions: All authors participated in the stages of the manuscript. Study concept and design: All authors. Acquisition

of data: T.R., T.J., G.B., A.S., and R.H. Analysis and interpretation of data: T.R., T.J., R.H., P.T., and A.D. Drafting manuscript: T.R., T.J., and R.H. Critical revision of the manuscript for important intellectual content: P.T., A.D., and R.H.. Study supervision: R.H.. Final approval of the version to be published: All authors. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved: All authors.

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REFERENCES

1. Bunchorntavakul C, Reddy KR. Review article: Malnutrition/sarcopenia and frailty in patients with cirrhosis. Aliment Pharmacol Ther 2020;51(1): 64–77.
2. Bojko M. Causes of sarcopenia in liver cirrhosis. Clin Liver Dis (Hoboken) 2019;14(5):167–70.
3. Ebadi M, Bhanji RA, Mazurak VC, et al. Sarcopenia in cirrhosis: From pathogenesis to interventions. J Gastroenterol 2019;54(10):845–59.
4. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. J Hepatol 2016;65(6):1232–44.
5. Dhaliwal A, Armstrong MJ. Sarcopenia in cirrhosis: A practical overview. Clin Med (Lond) 2020;20(5):489–92.
6. Nakaya Y, Okita K, Suzuki K, et al. BCAA-enriched snack improves nutritional state of cirrhosis. Nutrition 2007;23(2):113–20.
7. Montano-Loza AJ, Angulo P, Meza-Junco J, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. J Cachexia Sarcopenia Muscle 2016;7(2):126–35.
8. Hara N, Iwasa M, Sugimoto R, et al. Sarcopenia and sarcopenic obesity are prognostic factors for overall survival in patients with cirrhosis. Intern Med 2016;55(8):863–70.
9. Feito Y, Magal M. ACSM's Fitness Assessment Manual. Philadelphia: Wolters Kluwer, 2021.
10. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. Ann Intern Med 2009;151(4):W65–94.
11. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
12. Román E, García-Galcerán C, Torrades T, et al. Effects of an exercise programme on functional capacity, body composition and risk of falls in patients with cirrhosis: A randomized clinical trial. PLoS One 2016;11(3): e0151652.
13. Zenith L, Meena N, Ramadi A, et al. Eight weeks of exercise training increases aerobic capacity and muscle mass and reduces fatigue in patients with cirrhosis. Clin Gastroenterol Hepatol 2014;12(11):1920–6.e2.
14. Aamann L, Dam G, Borre M, et al. Resistance training increases muscle strength and muscle size in patients with liver cirrhosis. Clin Gastroenterol Hepatol 2020;18(5):1179–87.e6.
15. Limongi V, Dos Santos DC, de Oliveira da Silva AM, et al. Exercise manual for liver disease patients. World J Transpl 2016;6(2):429–36.
16. Macías-Rodríguez RU, Ilarraza-Lomelí H, Ruiz-Margáin A, et al. Changes in hepatic venous pressure gradient induced by physical exercise in cirrhosis: Results of a pilot randomized open clinical trial. Clin Transl Gastroenterol 2016;7(7):e180.
17. Román E, Torrades MT, Nadal MJ, et al. Randomized pilot study: Effects of an exercise programme and leucine supplementation in patients with cirrhosis. Dig Dis Sci 2014;59(8):1966–75.
18. Kruger C, McNeely ML, Bailey RJ, et al. Home exercise training improves exercise capacity in cirrhosis patients: Role of exercise adherence. Sci Rep 2018;8(1):99.
19. Lai JC, Dodge JL, Kappus MR, et al. A multicenter pilot randomized clinical trial of a home-based exercise program for patients with cirrhosis: The strength training intervention (STRIVE). Am J Gastroenterol 2021; 116(4):717–22.
20. Chen HW, Ferrando A, White MG, et al. Home-based physical activity and diet intervention to improve physical function in advanced liver disease: A randomized pilot trial. Dig Dis Sci 2020;65(11):3350–9.
21. Limongi V, dos Santos DC, da Silva AM, et al. Effects of a respiratory physiotherapeutic program in liver transplantation candidates. Transpl Proc 2014;46(6):1775–7.
22. Wallen MP, Keating SE, Hall A, et al. Exercise training is safe and feasible in patients awaiting liver transplantation: A pilot randomized controlled trial. Liver Transpl 2019;25(10):1576–80.
23. Pimentel CFMG, Amaral ACC, Gonzalez AM, et al. Six-minute walking test performance is associated with survival in cirrhotic patients. World J Hepatol 2021;13(11):1791–801.
24. Faustini Pereira JL, Galant LH, Rossi D, et al. Functional capacity, respiratory muscle strength, and oxygen consumption predict mortality in patients with cirrhosis. Can J Gastroenterol Hepatol 2016;2016: 6940374.
25. Berzigotti A, Albillos A, Villanueva C, et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: The SportDiet study. Hepatology 2017;65(4):1293–305.
26. Williams FR, Vallance A, Faulkner T, et al. Home-based exercise in patients awaiting liver transplantation: A feasibility study. Liver Transpl 2019;25(7):995–1006.
27. Lai JC, Tandon P, Bernal W, et al. Malnutrition, frailty, and sarcopenia in patients with cirrhosis: 2021 practice guidance by the American association for the study of liver diseases. Hepatology 2021;74(3): 1611–44. Erratum in: Hepatology. 2021 Dec;74(6):3563.