Digestive Diseases and Sciences (2024) 69:2655–2666
https://doi.org/10.1007/s10620-024-08447-0

ORIGINAL ARTICLE

Effectiveness of Exercise Interventions on Body Composition, Exercise Capacity, Fatigue, and Quality of Life in Patients with Liver Cirrhosis: A Meta-Analysis of Randomized Controlled Trials

Huei-Chi Hsieh[1] · Wen-Pei Chang[2,3] · Po-Jui Huang[4,5] · Chia-Hui Wang[3] · Yu-Huei Lin[6,7,8]

Received: 20 October 2023 / Accepted: 9 April 2024 / Published online: 24 April 2024

Abstract

Background Diminished muscle protein synthesis in cirrhosis leads to reduced strength and mass, impacting daily activities and overall quality of life.

Aims This study aimed to examine the effectiveness of exercise intervention in body composition, exercise capacity, fatigue, and quality of life in patients with liver cirrhosis.

Methods A systematic search of medical databases, including PubMed, Embase, Cochrane, and CINAHL, was executed from their inception to November 2022. The inclusion criteria were randomized controlled trials comparing exercise interventions with a control group that did not receive exercise interventions.

Results From the initially identified 2,565 articles, eight studies with a total of 220 patients were eligible for inclusion in this meta-analysis. According to the meta-analysis, exercise significantly improved the six-minute walk distance (6MWD) by 68.93 m (95% CI 14.29–123.57) compared to the control group. Furthermore, the subgroup analysis revealed that combing exercise with amino acid supplementation had a greater positive effect on the 6MWD (MD = 144.72, 95% CI 87.44–202.01). Exercise also significantly increased thigh circumference (MD = 1.26, 95% CI 0.12–2.39) and the thigh ultrasound average compression index (MD = 0.07, 95% CI 0.00–0.14). Moreover, exercise significantly decreased fatigue levels by 0.7 points in patients with liver cirrhosis (95% CI 0.38–1.03). However, no significant effects were observed on body mass index (BMI), fat mass, fat-free mass, and quality of life.

Conclusions Exercise can improve exercise capacity, thigh muscle thickness, and fatigue in patients with cirrhosis, but it does not have a significant impact on fat mass, BMI, or quality of life.

Keywords Liver cirrhosis · Exercise intervention · Body composition · Exercise capacity · Fatigue · Quality of life

✉ Yu-Huei Lin
gracelin@tmu.edu.tw

1 Department of Nursing, Hsinchu MacKay Memorial Hospital, Hsinchu, Taiwan

2 Department of Nursing, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan

3 School of Nursing, College of Nursing, Taipei Medical University, Taipei, Taiwan

4 Division of Gastroenterology, Wan Fang Hospital, Taipei Medical University, Taipei 110301, Taiwan

5 Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, 250 Wuxing St., Xinyi Dist., Taipei 11031, Taiwan

6 Post-Baccalaureate Program in Nursing, College of Nursing, Taipei Medical University, 250 Wu-Hsing Street, Taipei 11031, Taiwan

7 Research Center in Nursing Clinical Practice, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan

8 Department of Nursing, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan

Introduction

Cirrhosis is the final stage of chronic liver disease, marked by extensive hepatic fibrosis with possible consequences for hepatic function. The liver has an essential function in protein, carbohydrate, and fat metabolism [1]. Cirrhosis patients commonly show a reduction in muscle strength and muscle mass [2, 3], which is associated with decreased muscle protein synthesis [4]. As a result, this leads to a decreased ability to perform daily activities, ultimately impacting their quality of life [5–7].

The physiological changes resulting from liver cirrhosis encompass impaired hepatic function, electrolyte imbalances, and malnutrition [8]. Due to nutritional and metabolic abnormalities, patients with liver cirrhosis have an imbalance between protein synthesis and degradation [9], which can lead to changes in body composition and further complications such as sarcopenia and sarcopenic obesity [10, 11]. The reported incidence of sarcopenia in patients with liver cirrhosis ranges from 40 to 62% across studies [12]. Furthermore, sarcopenia has been found to be positively associated with increased mortality in liver cirrhosis patients [13, 14], and even increased mortality risk more than doubled in those with sarcopenia [2]. Therefore, measuring body composition is necessary for accurately evaluating the degree of malnutrition in cirrhotic patients [15].

Cirrhosis can lead to symptoms such as fatigue, abdominal discomfort, ascites, and edema [16–18]. Fatigue is a state of perception that arises from an abnormal perception of effort [19]. Patients with fatigue often experience persistent tiredness and a feeling of heaviness in their limbs, which can limit their motivation to engage in daily activities and social interactions [20]. The underlying mechanism of fatigue is not fully understood, as it may involve both peripheral and central factors [21]. However, interventions such as behavioral changes, medication, dietary adjustments, and exercise are commonly used to alleviate this symptom [22].

Exercise training can promote physical and mental health, and both aerobic and resistance exercises have been shown to improve liver fat metabolism [23, 24], as well as body composition, strength, and cardiorespiratory fitness in patients with chronic liver disease [25]. Moreover, exercise training can also alleviate fatigue in patients with chronic liver disease [26].

Aamann et al. published a systematic review and meta-analysis on exercise intervention in patients with liver cirrhosis in 2018, with the primary purpose of determining whether exercise intervention reduces mortality and serious adverse events [27]. However, more studies have been conducted in recent years, making it imperative to revise the existing data and conduct additional research on the effects of exercise interventions on fatigue and quality of life in patients with cirrhosis.

This meta-analysis seeks to evaluate the effectiveness of exercise interventions in improving body composition, exercise capacity, fatigue levels, and quality of life to provide a comprehensive analysis and evidence-based recommendations regarding patient care options for individuals with liver cirrhosis.

Methods

This meta-analysis was registered in PROSPERO (registration number: CRD42022376961) prior to initiating the study, and this study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. The PRISMA checklist can be found in the Online Resource 1.

Search Strategy

This study searched for relevant studies published before November 2022 in databases including PubMed, Embase, Cochrane, and CINAHL. The search focused on exercise interventions in patients with liver cirrhosis, with outcomes including body composition, exercise capacity, fatigue, and quality of life.

The search terms encompassed all subject terms and free terms of "liver cirrhosis," "exercise," "physical fitness," "fatigue," and "quality of life." The literature search was conducted in English without limitations on the earliest publication date. Additional details are provided in the Online Resource 2.

Study Selection

The current study was undertaken by two researchers who individually reviewed all the relevant literature and carried out a verification process. In instances when a disagreement emerged among the researchers and a consensus could not be achieved, the researchers sought the input of a third party to engage in discussion prior to arriving at a decision.

We only included studies that conducted randomized controlled trials (RCTs). The interventions in the RCTs for the experimental group could be exercise alone or exercise in combination with amino acid supplementation. In contrast, the control group got routine care. The outcome measures encompass numerous variables that are assessed to evaluate the effectiveness of the intervention.

Data Extraction

Two independent reviewers utilized a pre-decided data extraction chart to present the data from each study. The table included the author's name, nationality, year of publication, intervention for the experimental and control groups, sample size, type of exercise, duration, frequency, measurement tools, and outcomes. An outcome parameter was subjected to meta-analysis only if it had been reported in at least two studies. When a study had missing data, we contacted the corresponding author to request additional information. If an outcome measurement evaluates the parameter in a manner contrary to other assessment tools, we reverse the scores.

Risk of Bias Assessment

The Cochrane Collaboration's tool for assessing risk of bias (RoB) 2.0 was used in this study to evaluate the trial's quality. It is comprised of five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result, for quality assessment. We conducted a publication bias analysis using Egger's test within the Comprehensive Meta-Analysis Version 3.0 (Biostat Inc, Englewood, NJ, USA). If the *p*-value of Egger's test is greater than 0.1 and the confidence interval includes 0, it indicates no publication bias [28].

Statistical Methods

In this study, we used the Cochrane Review Manager software (RevMan 5.4) to perform statistical analysis. Mean difference (MD) was used for pooling studies with identical variables, and when the variables were not directly comparable, we employed the standardized mean difference (SMD).

The degree of heterogeneity was assessed using the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively [29]. Since the true effects of each study may differ and the weight of each study cannot be determined by the sample size alone, we used the random-effects model for all analyses.

Subgroup analysis was performed under the following circumstances: when different intervention methods were employed, or when similar parameters were measured using different assessment tools. This study is an analysis of data that have already been published, and thus it does not need approval from an ethics committee.

Results

Initially, a total of 739 relevant articles were identified. After removing 29 duplicated articles using EndNote X9 and eliminating four more duplicates manually, we screened the titles and abstracts of 706 articles, excluding 684 articles. Twenty-two articles met the inclusion criteria and were subjected to full-text assessment. Of these, eight articles were excluded because they were either trial register entries, posters, or abstracts lacking complete articles. Among the fourteen remaining articles, six were excluded due to the following reasons: two articles had both the experimental and control groups receiving exercise intervention; one article was not a randomized controlled trial, one article was not published in English, and two were review articles. As a result, eight randomized controlled trials were included in this meta-analysis, and the literature search process is presented in Fig. 1.

The total sample size throughout these eight randomized controlled trials consisted of 220 participants, with each individual study including a range of 17 to 40 participants. The average age of the participants was 58.02 years old with the Child–Pugh stages A, B, or C. The basic characteristics of the eight studies are presented in Table 1. The duration of exercise intervention was 8 weeks in two studies [30, 31], 12 weeks in five studies [32–36], and 14 weeks in one study [37]. Two studies included in this analysis used a combination of exercise and amino acid supplementation as the intervention [33, 34]. As for types of exercise, one study used resistance training [36]; five studies conducted aerobic exercises [30, 31, 33, 34, 37]; two studies had a combination of aerobic and resistance exercise [32, 35].

Risk of Bias and Quality

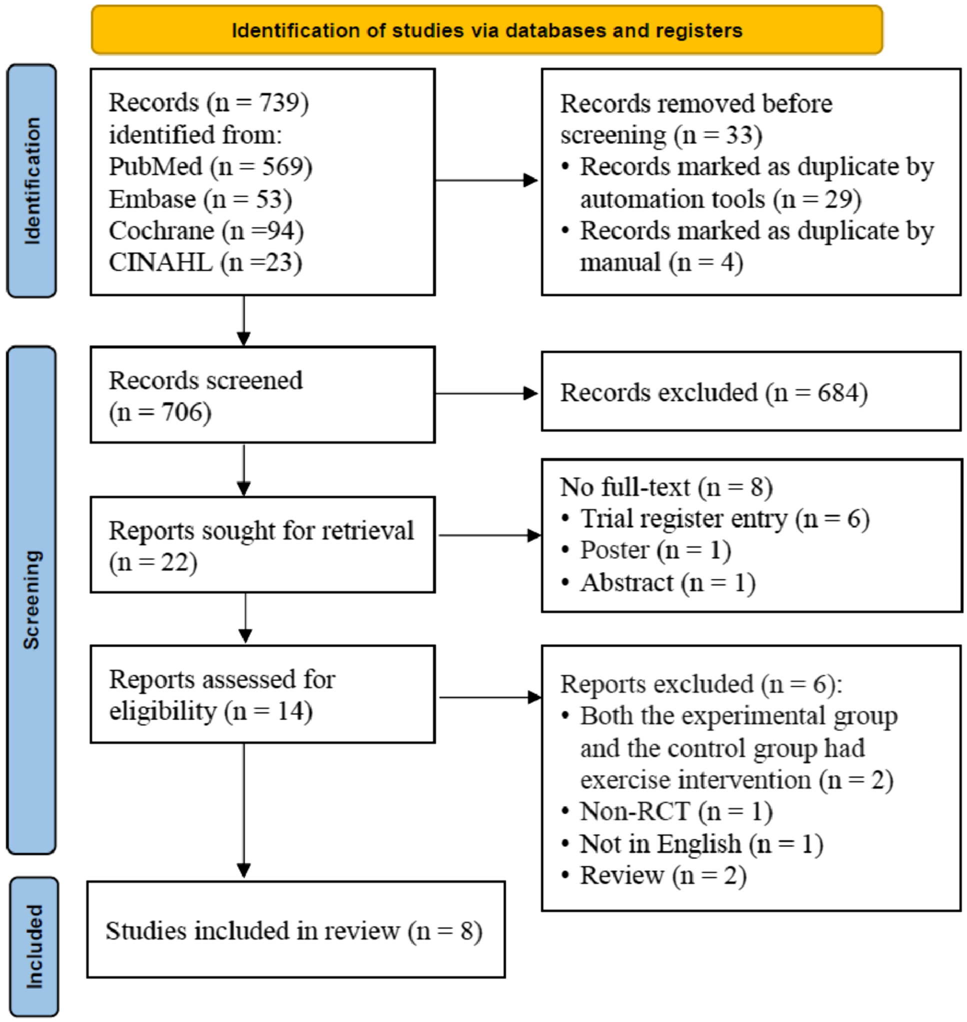
Using RoB 2.0, the literature's risk of bias was categorized into three levels: low risk, moderate risk, and high risk. Overall, the inadequate blinding of participants and assessors was the main source of risk of bias. Figure 2 displays the bias risk assessment results, while detailed information about bias across studies is available in Online Resource 3.

The *p*-values derived from all Egger's tests were greater than 0.1, indicating no statistically significant asymmetry in the funnel plot.

Body Composition

Body composition parameters, such as body mass index, thigh circumference, thigh muscle thickness, fat mass,

Fig. 1 The flow diagram of study selection



and fat-free mass reported in more than two studies, were incorporated into a meta-analysis.

Six studies provided BMI data [30, 33–37]. The effect of exercise intervention on BMI showed no statistically significant difference ($MD = 0.76$, 95% CI -0.16 to 1.69, $Z = 1.62$, $p = 0.11$, $I^2 = 0\%$) (Fig. 3).

Further subgroup analysis was conducted according to the interventions. The subgroup analysis revealed that there was no significant difference in BMI in either the sole exercise group ($MD = 0.86$, 95% CI -0.16 to 1.89, $Z = 1.65$, $p = 0.10$, $I^2 = 8\%$) or the exercise combined with amino acid supplementation group ($MD = -0.73$, 95% CI -4.22 to 2.76, $Z = 0.41$, $p = 0.68$, $I^2 = 0\%$).

Six studies [30–32, 34–36] reported thigh circumference values (Fig. 4). The findings of the meta-analysis indicated that the implementation of exercise intervention resulted in a statistically significant rise in thigh circumference ($MD = 1.26$, 95% CI 0.12 to 2.39, $Z = 2.16$, $p = 0.03$, $I^2 = 0\%$). Interestingly, further subgroup analysis showed that thigh circumference did not significantly increase in either the sole exercise group or the exercise combined with amino acid supplementation group.

Three studies reported data on thigh muscle thickness through the average compression index measured by ultrasonography [30, 31, 35]. The combined findings of the meta-analysis revealed a statistically significant increase in average compression index ($MD = 0.07$, 95% CI 0.00 to 0.14, $p = 0.04$, $I^2 = 0\%$) (Fig. 5).

Two studies measured fat mass [33, 36]. The pooled results of the meta-analysis indicated that the implementation of exercise intervention did not yield a statistically significant impact on fat mass ($SMD = 0.30$, 95% CI -0.29 to 0.90, $Z = 1.01$, $p = 0.31$, $I^2 = 0\%$) (Fig. 6). Both studies also provided data on fat-free mass [33, 36]. The meta-analysis results showed that the introduction of exercise intervention did not result in a statistically significant effect on fat-free mass ($SMD = 0.34$, 95% CI -0.25 to 0.94, $p = 0.26$, $I^2 = 0\%$) (Fig. 7).

Table 1 The characteristics of the included studies

Author, year, Country	Child–Pugh class	Average age (years)	Sample size (experimental/control)	Type of Exercise	Amino acids supplementation	Frequency	Duration	Outcomes
Aamann et al., 2020, Denmark	A/B	62	20/19	Resistance training	No	1 h/day, 3 days/week	12 weeks	6MWD, muscle strength, muscle mass, body composition anthropometry, and quality of life
Sirisunhirun et al., 2022, Thailand	A	56.5	20/20	Aerobic exercises, isotonic exercises	No	30 min/day, 4 days/week	12 weeks	6MWD, muscle mass, anthropometry, liver stiffness, spleen stiffness, and quality of life
Román et al., 2014, Spain	A/B	63	8/9	Aerobic exercises	leucine 10 g/day	1 h/day, 3 days/week	12 weeks	quality of life, exercise capacity, anthropometry, cognitive function, and ammonemia
Chen et al., 2020, USA	B/C	55.5	9/8	Aerobic exercises	amino acids 12 g/day	> 10,000 steps/day	12 weeks	6MWD, body composition, anthropometry, and quality of life
Román et al., 2016, Spain	A	62.5	14/9	Aerobic exercises, resistance training	No	30 min/day, 3 days/week	12 weeks	exercise capacity, body composition, anthropometry, and risk of falls
Macías-Rodríguez et al., 2016, USA	A/B	52	13/12	Aerobic exercises	No	40 min/day, 3 days/week	14 weeks	HVPG, quality of life, exercise capacity, nutritional status, ammonia levels, and safety
Kruger et al., 2018, USA	A/B	54.7	20/20	Aerobic exercises	No	30 min/day, 3 days/week	8 weeks	Peak VO_2, aerobic endurance, anthropometry, 6MWD, muscle mass, safety, and quality of life
Zenith et al., 2014, Canada	A/B	58	9/10	Aerobic exercises	No	30 min/day, 3 days/week	8 weeks	Peak VO_2, anthropometry, fatigue, depression, nutritional status, and quality of life

6MWD six-minute walk distance, *BMI* body mass index, *HVPG* hepatic venous portal gradient, VO_2, peak oxygen uptake

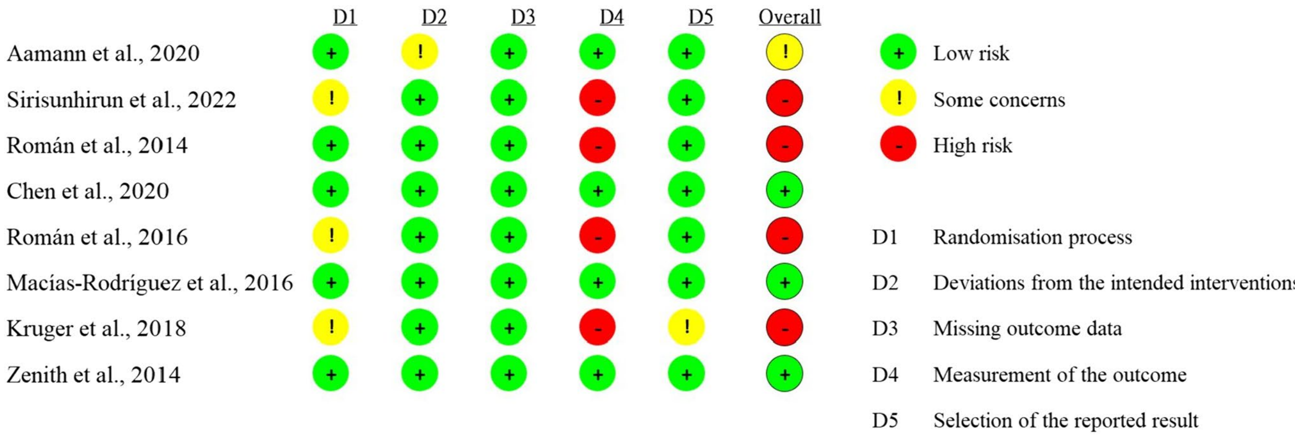


Fig. 2 Risk of bias assessment

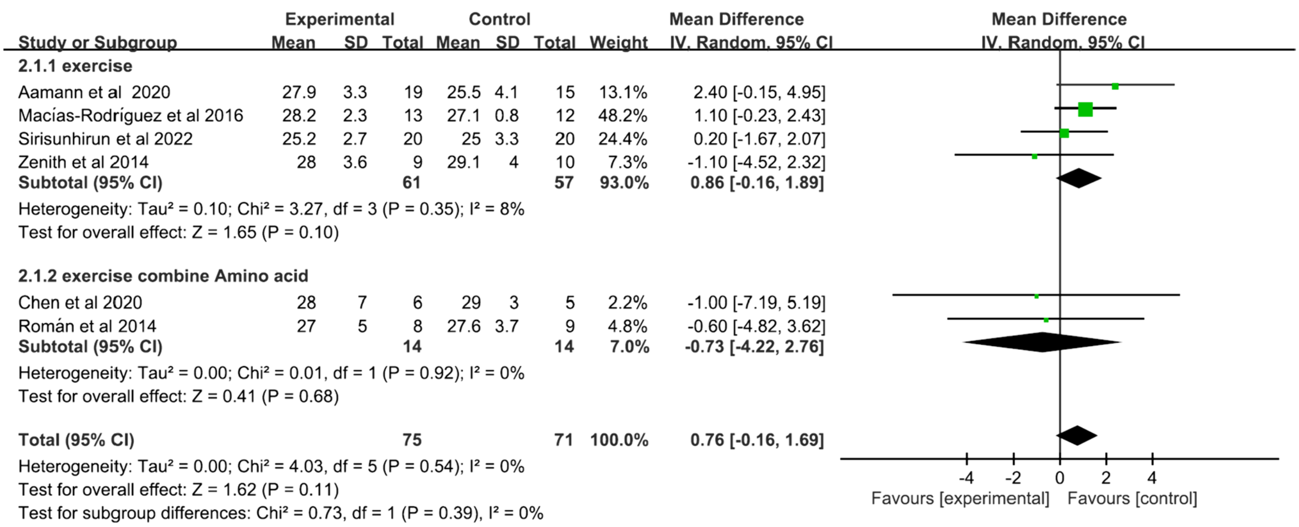


Fig. 3 Forest plot of exercise versus control group and exercise combined with amino acid versus control group, outcome: BMI (kg/m^2)

Exercise Capacity

Six studies presented the outcomes of six-minute walk distance (6MWD), allowing data aggregation for meta-analysis [30, 31, 33–36]. The experimental group receiving exercise intervention showed a significant increase of 68.93 m in 6MWD (95% CI 14.29 to 123.57, $Z = 2.47$, $p = 0.01$), but with moderate heterogeneity ($I^2 = 73\%$) (Fig. 8). Subgroup analysis was conducted based on the interventions of the experimental group, which involved either exercise alone or exercise combined with amino acid supplementation. The results showed that the improvement was not significant in the four studies that solely used exercise as the intervention [30, 31, 35, 36] (MD = 37.41, 95% CI − 15.20 to 90.01, Z = 1.39, $p = 0.16$, $I^2 = 61\%$). On the other hand, the analysis of the two studies [33, 34] that combined exercise with amino acid supplementation showed a significant increase in the 6MWD, with a mean difference of 144.72 m (95% CI 87.44 to 202.01, Z = 4.95, $p < 0.00001$, $I^2 = 0\%$).

Quality of Life

Seven studies reported numerical values regarding the impact of exercise intervention on quality of life [30, 31, 33–37] (Fig. 9). Among the seven studies, four used the Chronic Liver Disease Questionnaire (CLDQ) [30, 31, 35, 37]; two used the 36-item Short Form (SF-36) [34, 36], and one used the Sickness Impact Profile [33]. The pooled analysis revealed a tendency toward better scores in the exercise intervention group; however, this finding did not reach statistical significance (MD = 0.29, 95% CI − 0.01 to 0.58, $Z = 1.91$, $p = 0.06$, $I^2 = 0\%$). Subgroup analysis indicated no significant difference in the results across different subgroups, suggesting that the exercise had no significant

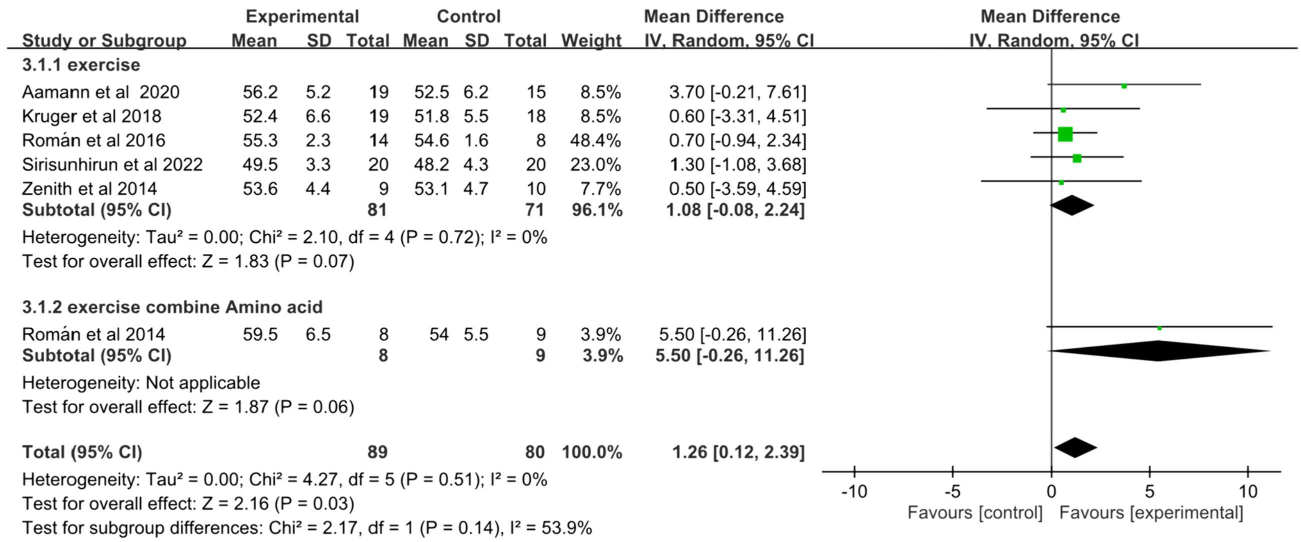


Fig. 4 Forest plot of exercise versus control group, outcome: thigh circumference

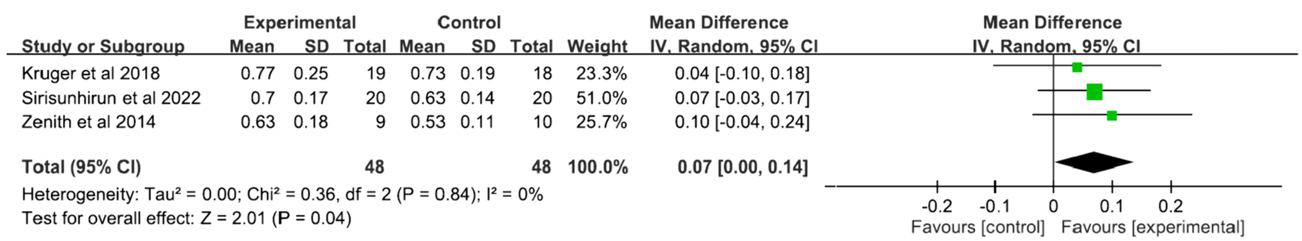


Fig. 5 Forest plot of exercise versus control group, outcome: average compression index

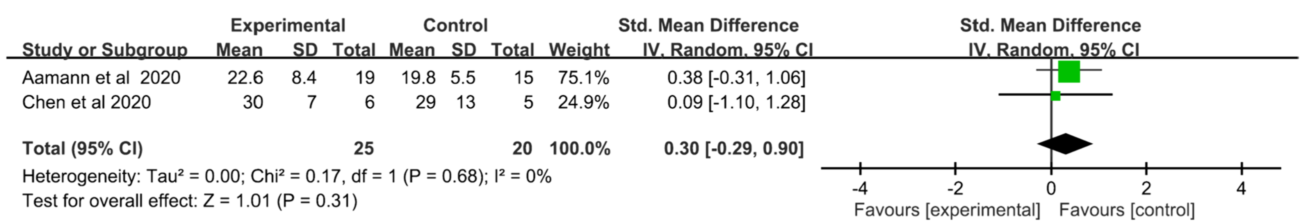


Fig. 6 Forest plot of exercise versus control group, outcome: fat mass

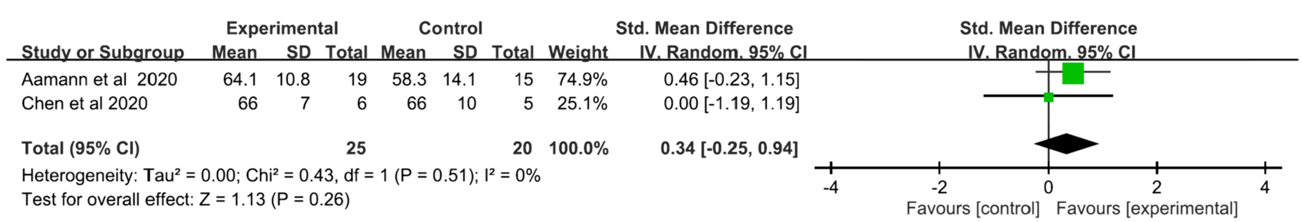


Fig. 7 Forest plot of exercise versus control group, outcome: fat-free mass

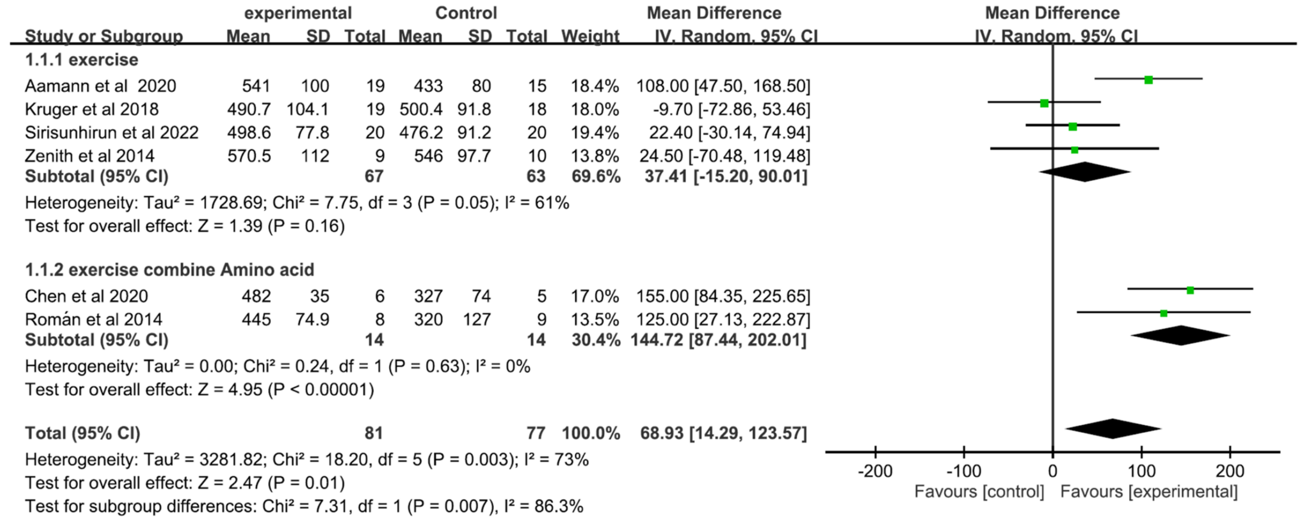


Fig. 8 Forest plot of exercise versus control group and exercise combined with amino acid versus control group, outcome: exercise capacity

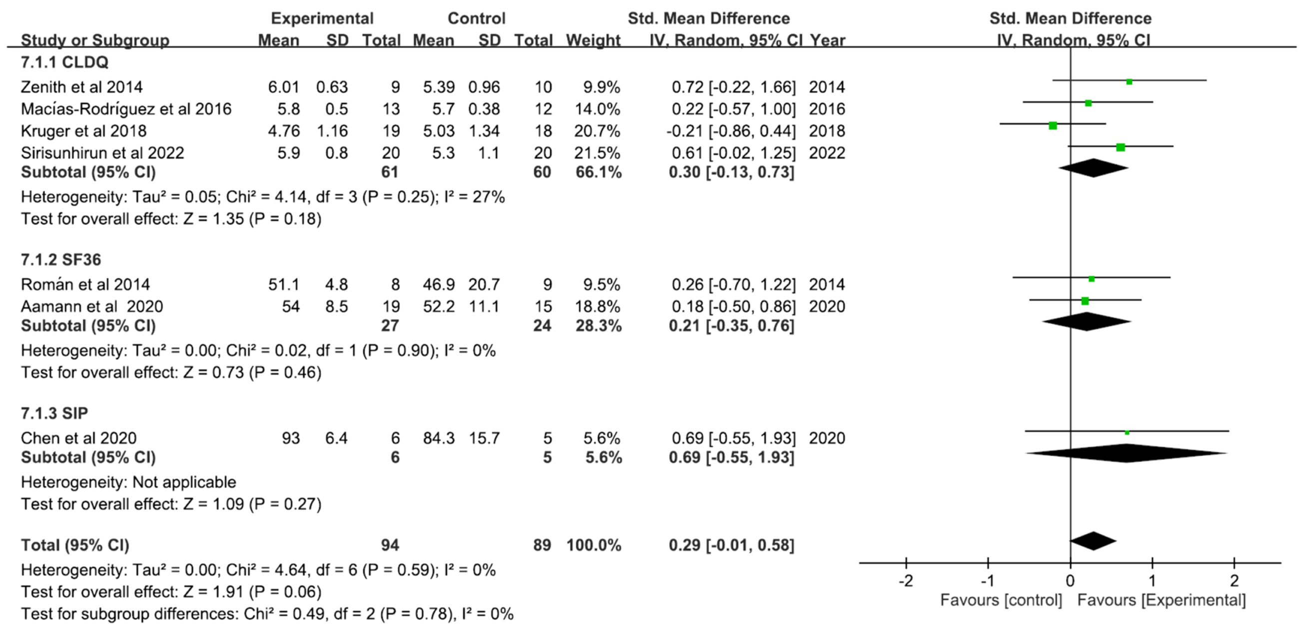


Fig. 9 Forest plot of exercise versus control group, outcome: quality of life

impact on quality of life regardless of the assessment tool used.

Fatigue

Four research studies used CLDQ and reported the levels of fatigue in people diagnosed with cirrhosis [30, 31, 35, 37]. Results indicated that the intervention group had significantly improved fatigue scores in comparison to the control group, demonstrating a mean increase of 0.70 points (95% CI 0.38 to 1.03, $Z = 4.23$, $p < 0.0001$). There is a statistically significant difference and no heterogeneity was observed ($I^2 = 0\%$), as shown in Fig. 10.

Discussion

The findings of this study indicate that exercise interventions have a notable positive effect on exercise capacity, thigh muscle thickness and thigh circumference, as well as a reduction in fatigue, among individuals with cirrhosis. However, there was no statistically significant disparity observed between the groups that received exercise

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Kruger et al 2018	4.14	1.35	19	4.16	1.68	18	11.0%	-0.02 [-1.01, 0.97]
Macías-Rodríguez et al 2016	5.8	0.9	13	4.9	0.2	12	42.2%	0.90 [0.40, 1.40]
Sirisunhirun et al 2022	5.6	0.9	20	4.9	1.1	20	27.4%	0.70 [0.08, 1.32]
Zenith et al 2014	5.62	0.71	9	4.93	0.93	10	19.4%	0.69 [-0.05, 1.43]
Total (95% CI)			**61**			**60**	**100.0%**	**0.70 [0.38, 1.03]**

Heterogeneity: Tau² = 0.00; Chi² = 2.66, df = 3 (P = 0.45); I² = 0%
Test for overall effect: Z = 4.23 (P < 0.0001)

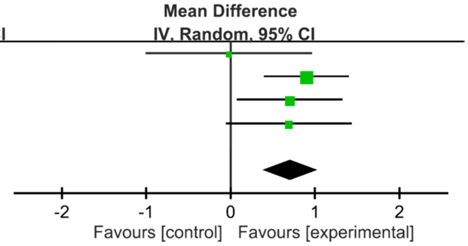


Fig. 10 Forest plot of exercise versus control group, outcome: fatigue

intervention and those that did not, when assessing body composition using BMI, fat mass, and fat-free mass. Subgroup analysis further showed that regardless of whether supplementing amino acids or not, short-term exercise intervention had no significant effect on BMI and fat mass in patients with liver cirrhosis.

This meta-analysis revealed that patients diagnosed with cirrhosis experienced a notable improvement in exercise capacity after engaging in exercise intervention, contrasting with the findings of the 2018 meta-analysis by Aamann et al. [27]. However, our subgroup analysis indicated that exercise intervention alone was not significantly effective in increasing the 6MWD among these patients. Notably, the combination of exercise with amino acid supplementation led to a marked enhancement in 6MWD. This is particularly relevant given the common occurrence of protein malnutrition in cirrhosis due to reduced liver function. Leucine, a branched-chain amino acid (BCAA), is emphasized for its role in stimulating muscle protein synthesis. Clinical trials and guidelines from the European Association for the Study of the Liver [8] recommend BCAA supplements, especially for advanced liver cirrhosis, to improve nutritional status, delay liver failure, and enhance overall health [38–40]. Our meta-analysis, however, included only two studies on exercise combined with amino acid supplementation, one with leucine [34] and the other with unspecified essential amino acids [33]. Furthermore, the potential impact of baseline differences in albumin levels, as observed in the study by Chen et al. [33], on the outcomes remains unaddressed, raising questions about the influence of such factors on our meta-analysis. While there is extensive research on the protein needs of cirrhosis patients, a clear consensus on estimating their nutritional requirements is still lacking, underscoring the need for further research in this area.

Assessing body composition in cirrhosis patients precisely is challenging due to fluid distribution imbalances across compartments. Anthropometry and bioelectrical impedance results may be affected by edema [41]. Using magnetic resonance imaging (MRI) or computed tomography to measure muscle mass would be ideal; however, only one study included in our analysis used MRI to measure lean mass, and their results showed a significant increase of 3% in whole-body lean mass (fat-free mass) [36].

The type and intensity of exercise among different studies may directly affect the results of muscle mass. Resistance exercise has demonstrated a better effect on muscle protein synthesis. However, in the studies included in this meta-analysis, five studies only used aerobic exercise as a therapeutic intervention. The intensity of aerobic exercise interventions was mostly moderate, such as 60–80% baseline peak VO_2 [30] or 60 to 80% of heart rate reserve [31, 37]. Aamann et al. employed resistance exercise, starting with 15 repetitions per session and gradually increasing the resistance while reducing the repetitions to 8 per set in the final two weeks; the exercise intensity was moderate [27]. Ideally, the inclusion of detailed measurement data on the intensity and duration of exercise interventions in each study would significantly enhance the comprehensiveness of the research. However, progress in this research is currently hampered by a lack of basic patient data, including body weight and oxygen consumption. In addition, detailed information on the specific exercise interventions utilized in the various studies is limited, which is also a significant challenge. The lack of data impedes accurate assessment of exercise interventions, thus constraining our ability to draw more nuanced conclusions from these studies.

Observations revealed a noticeable increase in thigh circumference. While thigh circumference may not serve as a direct indicator of thigh muscle mass, Zenith et al. employed ultrasound as a method to evaluate thigh muscle thickness alongside thigh circumference in the studies under consideration [30]. The findings of their investigation suggest that the observed increase in thigh circumference can be attributed to the growth of muscular tissue. Likewise, in the study by Aamann et al., the experimental group showed an increase in both thigh circumference and fat-free mass. This indirectly confirms that the rise in thigh circumference is associated with muscle growth [36]. Furthermore, the pooled data on average compression index indicated a significant increase in thigh muscle thickness.

Recent research has documented notable enhancements in both muscle strength and muscle mass among individuals diagnosed with cirrhosis and sarcopenia following a

24-week regimen of branched-chain amino acid (BCAA) supplementation [42]. Additionally, Hernández-Conde et al. observed enhanced muscle mass in patients with cirrhosis after a 12-week intervention involving exercise and BCAA supplementation, significantly higher than the control group receiving only exercise [43]. However, it is crucial to acknowledge that the existing literature presents divergent findings. In Mohta et al.'s research, it was observed that the addition of BCAA supplementation to standard treatment and exercise did not result in a significant increase in muscle mass in cirrhotic patients with sarcopenia [44]. Unfortunately, studies integrating amino acids with exercise interventions did not include measurements of muscle mass. Consequently, we are unable to conduct an analysis comparing the effectiveness of exercise alone versus exercise combined with amino acid supplementation on muscle mass.

Patients with liver cirrhosis often experience a substantial decline in their quality of life across various daily living domains [45, 46]. Symptoms like muscle cramps, while not life-threatening, can profoundly distress patients and deteriorate their quality of life [47]. In our study, although there was a positive trend observed in the experimental group, the improvement in quality of life did not reach statistical significance, aligning with the findings of Aamann et al. [27]. Notably, within the seven studies included in our meta-analysis that assessed quality of life, the study by Kruger et al. reported lower baseline quality of life scores in the experimental group [31], which could have influenced the overall outcome of our analysis. Upon re-evaluating this aspect and excluding the data from Kruger et al., the combined results from the remaining six studies indicated a significant enhancement in the quality of life. This finding suggests that exercise interventions are likely to positively impact the quality of life in cirrhosis patients.

Fatigue in individuals diagnosed with liver cirrhosis can be attributed to various factors, such as diminished hepatic functionality, metabolic abnormalities, insufficient nutritional intake, and the presence of other associated complications. Studies by Ahl et al. and Iwasa et al. have documented a reduction in cerebral blood flow in individuals with liver cirrhosis [48, 49], a phenomenon associated with the presence of fatigue [50]. We observed significantly reduced fatigue levels in the exercise intervention groups. Exercise promotes better blood circulation by enhancing cardiovascular health. This enhanced circulation ensures that vital organs, including the brain, receive an adequate supply of oxygen and nutrients, thereby potentially reducing fatigue and lethargy [51, 52]. Furthermore, engagement in exercise elicits the secretion of endorphins, an endogenous compound possessing analgesic attributes that enhance an individual's emotional state. Endorphins possess the capacity to mitigate the depressive symptoms commonly linked to chronic illnesses like cirrhosis, thereby indirectly ameliorating fatigue resulting from psychological distress [53, 54]. Patients with liver cirrhosis can indeed benefit from exercise as a means of reducing fatigue and enhancing their overall health if they approach it correctly. The type, duration, and intensity of exercise should be tailored to the health status and physical capabilities of the individual. However, investigating fatigue is a challenging task, given its subjective nature and absence of a clear and precise definition [55].

There are several limitations to this meta-analysis, including a limited number of studies and small sample sizes. The inclusion criteria or potential baseline imbalances in a single trial could influence the results of this meta-analysis. Additionally, the included studies varied in terms of the stage of liver cirrhosis, baseline nutritional status, type of exercise intervention, exercise intensity, and exercise duration, which may increase the heterogeneity of the results. Moreover, out of 220 participants, 15 (6.8%) were lost to follow-up.

In this meta-analysis, five studies included subjects with Child–Pugh class A and B; two studies involved subjects with Child–Pugh class A only; and only one study included a population with class B or C. Further research is needed to investigate the effects of exercise on decompensated liver cirrhosis patients.

Conclusion

Exercise intervention significantly improved exercise capacity and thigh muscle thickness in patients with liver cirrhosis. However, as a standalone intervention, exercise did not result in a significant enhancement of exercise capacity. To achieve better improvements in exercise capacity, it is recommended to combine exercise with amino acid supplementation. Furthermore, exercise significantly reduced fatigue levels, but improvements in quality of life, BMI, fat mass, or fat-free mass were not significant.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10620-024-08447-0.

Author's contribution Huei-Chi Hsieh: Writing—Original Draft, Formal analysis, Methodology, Data Curation. Wen-Pei Chang: Methodology, Writing—Review & Editing. Po-Jui Huang: Writing—Review & Editing. Chia-Hui Wang: Writing—Review & Editing. Yu-Huei Lin: Conceptualization, Formal analysis, Methodology, Data Curation, Writing—Review & Editing, Project administration.

Funding This research received no external funding from public, commercial, or non-profit organizations.

Declarations

Competing interest The authors declare that there is no conflict of interests in this study.

Institutional review board statement Not applicable.

Informed consent Not applicable.

References

1. Rui L. Energy metabolism in the liver. *Compr Physiol.* 2014;4:177–197.
2. Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG, et al. Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2012;10):166–73, 73.e1.
3. Jones JC, Coombes JS, Macdonald GA. Exercise capacity and muscle strength in patients with cirrhosis. *Liver Transpl.* 2012;18:146–151.
4. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. *J Hepatol.* 2016;65:1232–1244.
5. Orr JG, Homer T, Ternent L, Newton J, McNeil CJ, Hudson M et al. Health related quality of life in people with advanced chronic liver disease. *J Hepatol.* 2014;61:1158–1165.
6. Loria A, Escheik C, Gerber NL, Younossi ZM. Quality of life in cirrhosis. *Curr Gastroenterol Rep.* 2013;15:301.
7. Younossi ZM, Boparai N, Price LL, Kiwi ML, McCormick M, Guyatt G. Health-related quality of life in chronic liver disease: the impact of type and severity of disease. *Am J Gastroenterol.* 2001;96:2199–2205.
8. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. *J Hepatol.* 2019;70:172–193.
9. Charlton MR. Protein metabolism and liver disease. *Baillieres Clin Endocrinol Metab.* 1996;10:617–635.
10. Ebadi M, Bhanji RA, Mazurak VC, Montano-Loza AJ. Sarcopenia in cirrhosis: from pathogenesis to interventions. *J Gastroenterol.* 2019;54:845–859.
11. Schrager MA, Metter EJ, Simonsick E, Ble A, Bandinelli S, Lauretani F et al. Sarcopenic obesity and inflammation in the InCHIANTI study. *J Appl Physiol* 1985;2007(102):919–925.
12. Kim G, Kang SH, Kim MY, Baik SK. Prognostic value of sarcopenia in patients with liver cirrhosis: A systematic review and meta-analysis. *PLoS One.* 2017;12:e0186990.
13. Tandon P, Ismond KP, Riess K, Duarte-Rojo A, Al-Judaibi B, Dunn MA et al. Exercise in cirrhosis: Translating evidence and experience to practice. *J Hepatol.* 2018;69:1164–1177.
14. Meza-Junco J, Montano-Loza AJ, Baracos VE, Prado CM, Bain VG, Beaumont C et al. Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. *J Clin Gastroenterol.* 2013;47:861–870.
15. Figueiredo FA, De Mello Perez R, Kondo M. Effect of liver cirrhosis on body composition: evidence of significant depletion even in mild disease. *J Gastroenterol Hepatol.* 2005;20:209–216.
16. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol.* 2006;44:217–231.
17. Gabr RM, El Salmawy DA, Basheer MA, Khairy M, Elkholy SH. Relation between the severity of liver cirrhosis and neurological symptoms, nerve conduction study results, and motor unit number estimation. *J Viral Hepat.* 2021;28:1312–1318.
18. Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology.* 2009;49:2087–2107.
19. Swain MG. Fatigue in chronic disease. *Clin Sci (Lond).* 2000;99:1–8.
20. Swain MG, Jones DEJ. Fatigue in chronic liver disease: New insights and therapeutic approaches. *Liver Int.* 2019;39:6–19.
21. Cantor F. Central and peripheral fatigue: exemplified by multiple sclerosis and myasthenia gravis. *Pm r.* 2010;2:399–405.
22. Bhandari K, Kapoor D. Fatigue in Cirrhosis. *Journal of clinical and experimental hepatology.* 2022;12:617–624.
23. Diniz TA, de Lima Junior EA, Teixeira AA, Biondo LA, da Rocha LAF, Valadão IC et al. Aerobic training improves NAFLD markers and insulin resistance through AMPK-PPAR-α signaling in obese mice. *Life Sci.* 2021;266:118868.
24. Orci LA, Gariani K, Oldani G, Delaune V, Morel P, Toso C. Exercise-based Interventions for Nonalcoholic Fatty Liver Disease: A Meta-analysis and Meta-regression. *Clin Gastroenterol Hepatol.* 2016;14:1398–1411.
25. Smart NA, King N, McFarlane JR, Graham PL, Dieberg G. Effect of exercise training on liver function in adults who are overweight or exhibit fatty liver disease: a systematic review and meta-analysis. *Br J Sports Med.* 2018;52:834–843.
26. Frith J, Day CP, Robinson L, Elliott C, Jones DE, Newton JL. Potential strategies to improve uptake of exercise interventions in non-alcoholic fatty liver disease. *J Hepatol.* 2010;52:112–116.
27. Aamann L, Dam G, Rinnov AR, Vilstrup H, Gluud LL. Physical exercise for people with cirrhosis. *Cochrane Database Syst Rev*. 2018;12:Cd012678.
28. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj.* 1997;315:629–634.
29. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327:557–560.
30. Zenith L, Meena N, Ramadi A, Yavari M, Harvey A, Carbonneau M et al. Eight weeks of exercise training increases aerobic capacity and muscle mass and reduces fatigue in patients with cirrhosis. *Clin Gastroenterol Hepatol.* 2014;12:1920–6.e2.
31. Kruger C, McNeely ML, Bailey RJ, Yavari M, Abraldes JG, Carbonneau M et al. Home Exercise Training Improves Exercise Capacity in Cirrhosis Patients: Role of Exercise Adherence. *Sci Rep.* 2018;8:99.
32. Román E, García-Galcerán C, Torrades T, Herrera S, Marín A, Doñate M 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:e0151652.
33. Chen HW, Ferrando A, White MG, Dennis RA, Xie J, Pauly M 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;65:3350–3359.
34. Román E, Torrades MT, Nadal MJ, Cárdenas G, Nieto JC, Vidal S et al. Randomized pilot study: effects of an exercise programme and leucine supplementation in patients with cirrhosis. *Dig Dis Sci.* 2014;59:1966–1975.
35. Sirisunhirun P, Bandidniyamanon W, Jrerattakon Y, Muangsomboon K, Pramyothin P, Nimanong S et al. Effect of a 12-week home-based exercise training program on aerobic capacity, muscle mass, liver and spleen stiffness, and quality of life in cirrhotic patients: a randomized controlled clinical trial. *BMC Gastroenterol.* 2022;22:66.
36. Aamann L, Dam G, Borre M, Drljevic-Nielsen A, Overgaard K, Andersen H et al. Resistance Training Increases Muscle Strength and Muscle Size in Patients With Liver Cirrhosis. *Clin Gastroenterol Hepatol.* 2020;18:1179–87.e6.
37. Macías-Rodríguez RU, Ilarraza-Lomelí H, Ruiz-Margáin A, Ponce-de-León-Rosales S, Vargas-Vorácková F, García-Flores O

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:e180.
38. Marchesini G, Bianchi G, Merli M, Amodio P, Panella C, Loguercio C, et al. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. *Gastroenterology*. 2003;124:1792–801.
39. Yoshida T, Muto Y, Moriwaki H, Yamato M. Effect of long-term oral supplementation with branched-chain amino acid granules on the prognosis of liver cirrhosis. *Gastroenterol Jpn.* 1989;24:692–698.
40. Dam G, Ott P, Aagaard NK, Vilstrup H. Branched-chain amino acids and muscle ammonia detoxification in cirrhosis. *Metab Brain Dis.* 2013;28:217–220.
41. Heymsfield SB, Casper K. Anthropometric assessment of the adult hospitalized patient. *JPEN J Parenter Enteral Nutr.* 1987;11:36s–41s.
42. Singh Tejavath A, Mathur A, Nathiya D, Singh P, Raj P, Suman S et al. Impact of Branched Chain Amino Acid on Muscle Mass, Muscle Strength, Physical Performance, Combined Survival, and Maintenance of Liver Function Changes in Laboratory and Prognostic Markers on Sarcopenic Patients With Liver Cirrhosis (BCAAS Study): A Randomized Clinical Trial. *Front Nutr.* 2021;8:715795.
43. Hernández-Conde M, Llop E, Gómez-Pimpollo L, Fernández Carrillo C, Rodríguez L, Van Den Brule E et al. Adding Branched-Chain Amino Acids to an Enhanced Standard-of-Care Treatment Improves Muscle Mass of Cirrhotic Patients With Sarcopenia: A Placebo-Controlled Trial. *Am J Gastroenterol.* 2021;116:2241–2249.
44. Mohta S, Anand A, Sharma S, Qamar S, Agarwal S, Gunjan D et al. Randomised clinical trial: effect of adding branched chain amino acids to exercise and standard-of-care on muscle mass in cirrhotic patients with sarcopenia. *Hepatol Int.* 2022;16:680–690.
45. Shiraki M, Nishiguchi S, Saito M, Fukuzawa Y, Mizuta T, Kaibori M et al. Nutritional status and quality of life in current patients with liver cirrhosis as assessed in 2007–2011. *Hepatol Res.* 2013;43:106–112.
46. Dias Teixeira MC, de Fátima Gomes de Sá Ribeiro M, Strauss E. A new insight into the differences among non-cirrhotic and cirrhotic patients using the liver disease quality of life instrument (LDQOL). *Ann Hepatol*. 2005;4:264–71.
47. Marchesini G, Bianchi G, Amodio P, Salerno F, Merli M, Panella C, et al. Factors associated with poor health-related quality of life of patients with cirrhosis. *Gastroenterology*. 2001;120:170–8.
48. Iwasa M, Matsumura K, Kaito M, Ikoma J, Kobayashi Y, Nakagawa N et al. Decrease of regional cerebral blood flow in liver cirrhosis. *Eur J Gastroenterol Hepatol.* 2000;12:1001–1006.
49. Ahl B, Weissenborn K, van den Hoff J, Fischer-Wasels D, Köstler H, Hecker H et al. Regional differences in cerebral blood flow and cerebral ammonia metabolism in patients with cirrhosis. *Hepatology.* 2004;40:73–79.
50. Biswal B, Kunwar P, Natelson BH. Cerebral blood flow is reduced in chronic fatigue syndrome as assessed by arterial spin labeling. *J Neurol Sci.* 2011;301:9–11.
51. Seifert T, Secher NH. Sympathetic influence on cerebral blood flow and metabolism during exercise in humans. *Prog Neurobiol.* 2011;95:406–426.
52. Secher NH, Seifert T, Van Lieshout JJ. Cerebral blood flow and metabolism during exercise: implications for fatigue. *J Appl Physiol* 1985;2008(104):306–314.
53. Harber VJ, Sutton JR. Endorphins and exercise. *Sports Med.* 1984;1:154–171.
54. Khan S, Evans AA, Hughes S, Smith ME. Beta-endorphin decreases fatigue and increases glucose uptake independently in normal and dystrophic mice. *Muscle Nerve.* 2005;31:481–486.
55. Jason L, Brown M, Evans M, Anderson V, Lerch A, Brown A et al. Measuring substantial reductions in functioning in patients with chronic fatigue syndrome. *Disabil Rehabil.* 2011;33:589–598.