European Journal of Physical and Rehabilitation Medicine 2024 February;60(1):122-9
DOI: 10.23736/S1973-9087.23.08130-3

ORIGINAL ARTICLE

The influence of prehabilitation in patients with liver cirrhosis before liver transplantation: a randomized clinical trial

Ľubomír SKLADANÝ [1, 2], Dávid LÍŠKA [3] *, Daniel GURÍN [4], Pavol MOLČAN [1], Roman BEDNÁR [5], Janka VNENČÁKOVÁ [1], Tomáš KOLLER [6]

[1]Division of Hepatology, Gastroenterology and Liver Transplant (HEGITO), Second Department of Internal Medicine, Faculty of Medicine, F.D. Roosevelt Teaching Hospital, Slovak Medical University, Banská Bystrica, Slovakia; [2]Second Department of Internal Medicine, Faculty of Medicine, P.J. Safarik University, Košice, Slovakia; [3]Department of Physical Education and Sports, Faculty of Arts, Matej Bel University, Banská Bystrica, Slovakia; [4]Faculty of Healthcare, Slovak Medical University in Bratislava, Banská Bystrica, Slovakia; [5]Department of Physiatry, Balneology and Rehabilitation, F.D. Roosevelt Teaching Hospital, Slovak Medical University, Banská Bystrica, Slovakia; [6]Subdivision of Gastroenterology and Hepatology, Fifth Department of Internal Medicine, Faculty of Medicine, University Hospital, Comenius University, Bratislava, Slovakia

*Corresponding author: Dávid Líška, Faculty of Arts, Matej Bel University, Tajovského 40, 974 01 Banská Bystrica, Slovakia.
E-mail: david.liska27@gmail.com

ABSTRACT

BACKGROUND: The high prevalence of liver cirrhosis in Slovakia leads to a great need for transplant treatment. The outcome of liver transplantation is influenced by several factors.
AIM: The main objective of this study is to test the effectiveness of prehabilitation compared to standard of care.
DESIGN: Prospective, double-arm, randomized, open-registry study.
SETTING: Patient in F. D. Roosevelt Teaching Hospital, Slovakia, Banská Bystrica.
POPULATION: The participants consisted of patients with liver cirrhosis (55 men, 25 women).
METHODS: The patients were randomized to the active prehabilitation group (N.=39) or the standard of care group (SOC) (N.=41). SOC represents the standard of care for patients prior to liver transplantation, consisting of a formal oral interview lasting 30 minutes. In addition to SOC, each patient with decompensated liver cirrhosis also underwent a prehabilitation intervention that included rehabilitation and nutrition support. Patients completed the exercises under the supervision of a physician during hospitalisation.
RESULTS: After one month, the liver frailty index improved in the prehabilitation group (P=0.05). No improvement in MELD (Model of End Stage Liver Disease) was found in the group that underwent the prehabilitation program (P=0.28), and no improvement was found in the Child–Pugh score after one month (P=0.13). In the prehabilitation groups compared with the SOC group, differences were not found in the MELD score (P=0.11). Better clinical outcomes according to the Child-Pugh score was found for the prehabilitation group compared with the SOC group (P=0.02). According to LFI, there was no difference between the groups (P=0.26). Very low adherence was found after three months. Only three patients in the SOC group and six patients in the prehabilitation group came to the check-up. Due to low adherence after 3 months in patients with liver cirrhosis, it is not possible to make an adequate comparison between groups after three months.
CONCLUSIONS: Despite the great effort to maintain adherence, it was not possible to draw a conclusion about the effectiveness of prehabilitation in patients before liver transplantation compared to standard of care because the main problem in Slovak patients with liver cirrhosis is low adherence. More studies are needed to identify the barriers that lead to low adherence in patients with liver cirrhosis.
CLINICAL REHABILITATION IMPACT: A promising result was found due to improvement of the Liver Frailty Index and the Child-Pugh Score after one month in the prehabilitation group.

(*Cite this article as:* Skladaný Ľ, Líška D, Gurín D, Molčan P, Bednár R, Vnenčáková J, *et al*. The influence of prehabilitation in patients with liver cirrhosis before liver transplantation: a randomized clinical trial. Eur J Phys Rehabil Med 2024;60:122-9. DOI: 10.23736/S1973-9087.23.08130-3)

KEY WORDS: Prehabilitation; Exercise; Frailty; Liver transplantation.

Liver cirrhosis is the final stage of many liver diseases and is associated with significant morbidity and mortality, for which definitive treatment is liver transplantation.[1] Liver cirrhosis, which is recommended in clinical practice as advanced chronic liver disease (ACLD), is currently the most common cause of death among young people in Slovakia. Advanced decompensated ACLD (dACLD) is the most prevalent in the Slovakia.[2] At this stage, in addition to the liver, many other organs and systems are affected, including the neuromuscular and cardiorespiratory systems.[3]

Malnutrition and musculoskeletal damage, manifested primarily as sarcopenia, has a complex pathogenesis. Sarcopenia is consensually defined by reduced muscle mass and function, along with a structural change in skeletal muscle.[4-7] The European Working Group on Sarcopenia defines sarcopenia as a progressive, generalized loss of muscle mass with associated functional losses.[8] The result is a disorder of metabolism, growth, and muscle function.[9, 10] Severe muscle wasting is one of the most common and often hidden complications in patients with liver cirrhosis, negatively affecting survival, quality of life, and response to stressors such as infections and surgeries.[10]

Sarcopenia is considered a specific complication of ACLD and is associated with poor liver transplant outcomes.[10] The situation in the intervention area is complicated by the reduction in exercise capacity and the reduced muscle strength associated with malnutrition and sarcopenia.[11] Reduced performance in patients with liver cirrhosis is associated with poorer quality of life.[12, 13] Sarcopenia is associated with frailty syndrome in patients with liver cirrhosis.[14, 15] Frailty is a geriatric syndrome characterized by a decrease in physiological reserve and function in multiorgan systems.[16-19] Frailty syndrome includes a complex manifestation in the form of weakness, low physical activity, exhaustion, and unintentional weight loss. Frailty predicts increased morbidity and mortality in patients with liver cirrhosis. Nutritional intervention and rehabilitation are the cornerstones of proper management of patients with liver cirrhosis, malnutrition, sarcopenia, and frailty syndrome. Exercise in patients with liver cirrhosis can improve muscle mass and function and favourably affect prognosis.[20] Prehabilitation is defined as the process of increasing functional capacity before surgery with the aim of reducing postoperative morbidity and mortality.[21] Prehabilitation is a treatment that focusses on preparing the patient before surgery, in this case, a liver transplant. Prehabilitation includes exercise as well as psychological and nutritional support.[22-24] Liver transplantation is the only treatment method for many forms of dACLD with 5- and 10-year survival rates of 80% and 60%, respectively.[25, 26] Liver transplantation offers lasting hope for a cure in patients with end-stage liver disease.[27] The time period of the LT waiting list provides an opportunity to prehabilitate and improve patients' physical condition.[28]

Therefore, the main objective of our study is to determine the effectiveness of prehabilitation compared with standard treatment in patients with ACLD who are registered or potentially registered on the waiting list for liver transplantation. The secondary objective is to compare the effectiveness of prehabilitation with the standard of care from the perspective of the quality of life.

Materials and methods

Prospective, double-arm, randomized, open-registry study (NCT04767945). Patients were placed on the registry, which is known as RH7. All consenting adult patients who are hospitalized with ACLD/dACLD are registered in RH7 in Slovakia. The RH7 registry was established in 2014 and is applied to the Department of Hepatology, Gastroenterology and Transplantation, II. Internal Clinic of the Slovak Medical University (HEGITO). For this study (PREHAB-RH7), new patients in RH7 who did not have contraindications to liver transplantation were selected. Patients had to agree and sign an informed consent to participate in the study. Only active patients registered in RH7 were included in the study. Patients who did not sign an informed consent were not included in the study. Patients in a coma and those who had a severe degree of liver encephalopathy, high temperature, acute injury, a posttraumatic condition associated with functional deficit, peripheral and central paresis, and conditions after sudden stroke were excluded from the study. After hospitalization and enrolment and in the absence of exclusion criteria, patients were assigned to randomization. The patients were randomized to the active prehabilitation arm or the standard of care (SOC) group (Figure 1). The allocation was concealed and carried out by an administrative worker. Randomization software was used for the randomization. After entry into the study, demographic, clinical, anthropometric and laboratory parameters were investigated to determine the aetiology and stage of ACLD, nutritional status, sarcopenia and frailty (Table I). Adherence to exercise was checked using the exercise calendar that the patient received when entering the study. The study protocol was in accordance with the ethical guidelines of the Declaration of Helsinki. Ethical approval was given by the ethics committee of the Roosevelt Hospital in Banská Bystrica under number 15072. None of the patients were institutionalized.

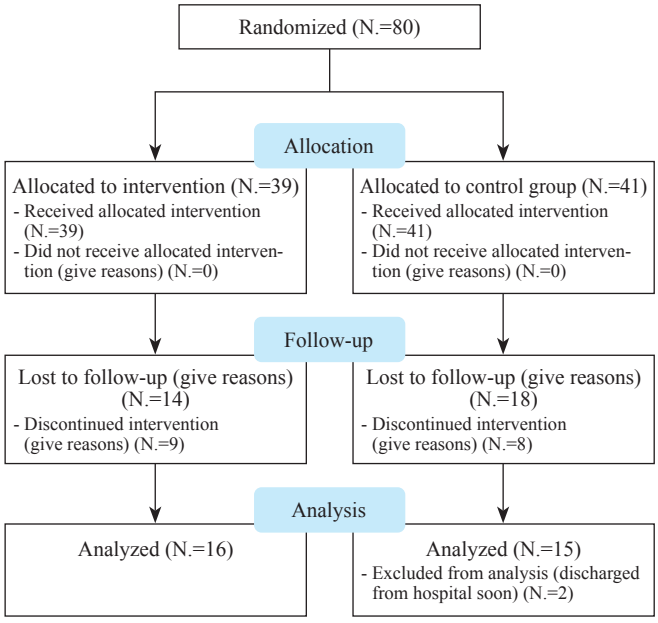

Figure 1.—Flow diagram of the study.

The sample

The participants consisted of patients with liver cirrhosis (55 men, 25 women). The study participants were divided into a prehab group (N.=39, 24 men and 15 women) and a standard of care group (N.=41, 31 men and 10 women). The baseline characteristics are listed in Table I. The flow diagram of the study is shown in Figure 1.

Standard of care (control group)

SOC represents the standard of care for patients prior to liver transplantation, which consisted of a formal oral interview lasting 30 minutes. The patient was instructed regarding an optimal lifestyle and exercise. Nutrition information included the 3- to 4-hour frequency of meals and sipping at night. For each day, the patients had two bottles of Nutridrink at their disposal, the consumption of which was recommended between meals. Sipping was calculated to add up to the daily energy requirement of 600 kcal and proteins to cover the night-time snack and the interval between the main meals. An oral nutritional supplement was recommended in the form of 'sipping' to complement the source of energy and protein provided by regular meals and to facilitate the observance of the recommended maximum intervals between meals and snacks. Liquid polymeric (1.5 kcal/mL) preparations with total daily volumes of 400 and 600 mL, respectively, were suggested to cover an energy intake of 600 kcal between meals. Education about proper nutrition also included information on food selection with a focus on proteins. Regarding physical activity, patients received oral and written instructions on the importance of regular physical exercise and the importance of muscle mass and muscle strength, sarcopenia and its consequences for health and the possible impact of regular exercise on prevention and treatment. In addition to oral instructions, the patient received a list of safe exercises (Supplementary Digital Material 1: Supplementary Text File 1). The patients were recommended 15-20 minutes of physical activity at least three times per week.

Prehabilitation (intervention group)

In addition to SOC, each patient with decompensated cirrhosis also underwent a prehabilitation intervention. The patients performed exercise under the supervision of a physiatrist during hospitalization. Exercise was applied according to the initial examination by the physician, taking into account the patient's condition and a personal-

TABLE I.—*Baseline characteristics of the whole group.*

Characteristics	Prehab (N.=39)	Standard (N.=41)	All (N.=80)	P value
Gender (F)	15	10	25	-
Age	56.51±11.9	55.29±13.2		
Height	172±8.69	173.28±6.5	172.88±7.91	0.93
Weight	78.61±20.34	81.18±16.09	80.58±18.33	0.48
BMI	26.46±6.09	27.07±5.45	26.78±5.69	0.66
MELD	15.78±5.60	18.83±6.84	17.41±6.35	0.03
CHP	7.61±2.13	8.40±2.37	8.04±2.27	0.15
LFI	4.18±0.92	4.21±1.02	4.19±0.97	0.95
Etiology of cirrhosis				
ALD	21 (53.85%)	22 (53.65%)	43 (53.75%)	
Other (NASH, HBC, HCV, PBC, PSC)	18 (46.15%)	19 (46.35%)	37 (46.25%)	

F: female; BMI: Body Mass Index; MELD: The Model for the End-Stage Liver Disease; CHP: Child-Pugh score; LFI: Liver Frailty Index; ALD: alcoholic liver disease; NASH: non-alcoholic steatohepatitis; HBC: hepatitis B; HCV: hepatitis C; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis.

ized approach considering functional status. The exercise included a warm-up phase (5-10 min), followed by low-intensity exercise, which was a combination of simple resistance exercises and low-intensity aerobic exercise. Patients exercise 15 to 20 minutes at least three times a week.

The Model for End-Stage Liver Disease (MELD) Score

The MELD score was developed to predict prognosis in a particular clinical setting. However, due to its application, objectivity, and prediction capability, it has become widely accepted as a survival predictor of liver cirrhosis.[29, 30] The score is based on objective parameters and predicts survival at a higher value (from an interval of 6-40), meaning a worse prognosis (*e.g.* patients with a MELD score greater than 15 should be considered for liver transplantation; A MELD score over 21 represents a severe variant of alcoholic hepatitis.)

The Child-Pugh score (CPS) and ascites classification

This rating developed four decades before MELD was aimed at the same goal of predicting liver cirrhosis survival.[31] In contrast to a purely laboratory MELD, the parameters incorporated into the CPS are also clinically evaluated (ascites and encephalopathy). The final score is expressed by both a class number and a score/number:

- CPS class A/5 points = compensated;
- CPS B/8 = mild decompensation;
- CPS C/15 = severe cirrhosis decompensation.

Ascites, an accumulation of fluids in the abdomen, was classified as zero if it was not present on the ultrasound, grade 1 if detected by ultrasound only (not apparent on physical examination), grade 2 if detectable on physical examination and confirmed by ultrasound and grade 3 or tense if the skin of the distended abdomen was tight.

Liver Frailty Index (LFI)

The Liver Frailty Index (LFI) is a diagnostic modality of the guideline-recommended toolkit for physical frailty of liver cirrhosis patients.[32] The LFI is composed of three performance-based tests — grip strength, chair stands, and balance test.[32] The LFI defines frailty as a cumulative deficit in the functional condition.[15] The LFI score can be calculated using an online calculator (http://liverfrailtyindex.ucsf.edu). patients are classified as robust, prefrail and frail according to their index (index <3.2, robust; 3.2–4.5, prefrail; and >4.5, frail). In general, LFI represents a reliable test (correlation coefficient = 0.93) and is a valid examination of liver cirrhosis.[33]

EuroQOl-5D (EQ-5D)

EuroQOl-5D (EQ-5D) is questionnaire to measure quality of life (QOL), which has been validated in various diseases.[34-36] It has been demonstrated that EQ-5D is valid in liver patients, which is comparable to our cohort.[37] EQ-5D measures five domains underlying quality of life: mobility, self-care, daily activities, pain, anxiety and depression, together with the patient's assessment of perceived health status on a visual analogue scale. The final EQ-5D is defined as a score of 0 to 100 for the overall quality of life of an individual. The owner of the EQ-5D kindly granted the permission for the use of HEGITO.

Statistical analysis

All baseline characteristics were recorded in MS Excel 2016®. Descriptive statistics and confirmation of differences between the obtained values were performed in SPSS®. The normality of the data was confirmed with the Shapiro-Wilk Test. To verify the statistical significance of differences between groups, a two-sample Student's *t*-test and Wilcoxon test were used, according to result of the normality test. To verify differences between groups, the independent-samples *t*-test and Mann-Whitney Test were used.

Results

The overall mean age of the group was 55.29±13.2. The MELD score in patients with liver cirrhosis was 26.78±5.69, and the Child-Pugh score was 8.04±2.27. The LFI was at the level of 4.19±0.97 (Table I).

Outcomes were measured after one and three months (Figure 1). After one month, the liver frailty index improved in the prehabilitation group (P=0.05). No improvement in MELD was found in the group that underwent the prehabilitation program (P=0.28), and no improvement was found in the Child-Pugh score after one month (P=0.13). QOL was not affected after one month of prehabilitation (P=0.30).

The LFI in the SOC group did not improve after one month (P=0.46). No improvement was found after one month in the SOC group according to the MELD (P=0.46) or the Child-Pugh score (P=0.31). Changes in quality of life did not occur in patients in the SOC group (P=0.39) (Table II).

No differences were found in the MELD score in the prehabilitation group compared with the SOC group (P=0.11). Better clinical outcomes according to the Child-Pugh score was found in the prehabilitation group

TABLE II.—*Outcomes of patients in the prehab study.*

Parameters	Period	Prehab group Mean±SD	P value	SOC group Mean±SD	P value	Between-group P value
MELD	Baseline	15.78±5.60	0.28	18.83±6.84	0.46	0.11
	After 30 days	14.84±4.91		18.67±8.0		
CHP	Baseline	7.61±2.13	0.13	8.40±2.37	0.31	0.02
	After 30 days	6.70±1.83		8.44±1.83		
LFI	Baseline	4.18±0.92	0.05	4.21±1.02	0.17	0.26
	After 30 days	3.72±0.76		4.09±0.95		
QOL	Baseline	8.00±4.42	0.30	8.56±5.36	0.39	0.42
	After 30 days	8.00±3.65		8.67±5.27		

MELD: model for end-stage liver disease; CHP: Child-Pugh score; LFI: Liver Frailty Index; QOL: quality of life.

(P=0.02). According to LFI, there was no difference between the groups (P=0.26). No differences were found in QOL (P=0.42) (Table II).

Very low adherence was found after three months. Only three patients in the SOC group and six patients in the prehab group came to the check-up. Due to low adherence after three months in patients with liver cirrhosis, it is not possible to make an adequate comparison between the groups after three months.

Discussion

In the last decade, frailty has emerged as a strong predictor of clinical outcomes in patients with cirrhosis and in those requiring liver transplantation. Therefore, the main objective of the study was to test the effectiveness of prehabilitation compared with that of standard care. In the group of patients who underwent prehabilitation, an improvement in the liver frailty index was found after one month. This improvement appears to be beneficial due to the short intervention time and may represent a great benefit to patients. If it were possible to maintain better adherence in patients after three months, it would probably be possible to find better results according to the LFI.

In the first study, we focused on testing adherence to oral supplementation in patients with liver cirrhosis.[38] The sample consisted of patients with ACLD, the same as in this study. Adherence to oral supplementation decreased significantly after hospital discharge and was associated with worse outcomes. Subsequently, we were looking for a way to achieve greater adherence in patients, which led to the creation of this study. In the first study, nutrition education was carried out by a nutrition nurse. We hypothesized that if we supplement the nutrition nurse's education with education from doctors about exercise during hospitalization, it will help us to achieve better clinical results. This assumption was not confirmed, and low compliance was found in the first and second follow-up, despite our best effort. It is difficult to determine the main reason why patients do not follow the recommended procedures and others necessary to identify the barriers that lead to the justification of compliance in patients with liver cirrhosis in Slovakia. Identification of the barriers that prevent patient adherence to recommended practices will lead to better patient outcomes. There may be several reasons for the lower patient adherence. One of the main reasons may be the weak relationship between the patients and the doctor, which is caused by the lack of time and space to develop a therapeutic relationship. Another reason for low adherence can be assumed to be high alcohol consumption; alcohol dependence will affect several of patients' cognitive functions, and it is possible to assume that it will significantly affect the ability to heal.

In fact, exercise in patients with advanced cirrhosis has been controversial due to the theoretical risk of increased portal pressure during exercise and the potential damage induced by variceal bleeding, liver encephalopathy or worsening of muscle breakdown in these patients with marked sarcopenia. The purpose of the review by Locklear *et al.*[11] was to evaluate the effectiveness of exercise in patients with end-stage liver disease. Seven studies were included in the analysis. In most studies, an improvement in oxygen consumption was found. In two of the three studies, an improvement was found according to the 6-min walking test. In cirrhotic patients, exercise has been shown to improve muscle mass and strength, aerobic capacity, fatigue and quality of life.[39] In our study, an improvement was found according to the LFI in the prehabilitation group, which is consistent with the results of other studies.

Poor physical fitness and functional status compromise postoperative functional recovery and lead to adverse postoperative outcomes, including complications, prolonged hospital stay and mortality.[20] In patients with cirrhosis, cardiac function and pulmonary gas exchange are often

altered. In addition to liver dysfunction, patients have reduced tolerance and reduced maximum oxygen consumption during exercise. The most significant decrease in VO_2 occurs in patients with severe liver dysfunction.[40] Furthermore, exercise oxygen consumption is not only correlated with the severity of liver disease but is also independently associated with lower survival after liver transplantation.[41, 42] Physical performance affects the quality of life of patients with liver cirrhosis.[12]

Low adherence was also found in a study by Lai[43] in which the effectiveness of a strength training intervention (STRIVE) was tested in patients with liver cirrhosis. The exercise program consisted of 12 weeks, a 30-minute strength training video, plus a health coach or standard of care (SOC). Fifty patients with liver cirrhosis were randomly divided into a group that practiced strength exercises according to a video + coach and a group that received standard treatment (N.=25). After 12 weeks, the liver frailty index improved from 3.8 to 3.6 in the intervention group and from 3.7 to 3.6 in the standard treatment group. The CLDQ score improved from 4.6 to 5.2 in the intervention group and did not change in the standard treatment group. Low adherence was found in the intervention group, only 14% during 10-12 weeks.

A study by Wang *et al.*[32] evaluated the effectiveness of a prehabilitation program in patients (N.=70) before liver transplantation. Similarly to our study, the control group consisted of patients who completed standard of care (N.=34). The median Charlson's comorbidity index was higher in the group that completed the prerehabilitation program (4 *vs.* 3, P=0.03). There was a reduction in overall morbidity (30% *vs.* 52.9%, P=0.02) and social problems (P=0.03). The Quality-of-Life survey showed an improvement in social well-being. Lai *et al.*[43] evaluated the effectiveness of frailty in patients before liver transplantation. Frailty in patients was evaluated similarly using the liver frailty index, as in our study. In addition, a 6-minute Walking Test and a walking speed test were used. The study included 517 patients (59% male, median age 61 years, and an end-stage liver disease score model of 12. The frailty index was influenced by age, sex and liver-related parameters, but not by the end-stage liver disease model. Patients with non-alcoholic fatty-liver disease and alcohol-related cirrhosis had worse frailty metrics according to all instruments. Furthermore, in patients with liver cirrhosis, a positive effect of prehabilitation was found to improve the liver frailty index and the 6-min test in adherent patients. A median improvement in LFI of 0.3 in diseased patients was associated with better compliance with survival with physical therapist visits (hazard ratio 0.35 [0.18-0.67] for two visits and a risk ratio 0.54 [0.31–0.94] for three visits) was independently associated with increased survival.

The effectiveness of prehabilitation was also evaluated in a study by Dunne *et al.*[44] In this study, the effectiveness of a 4-week supervised exercise program (12 sessions) was evaluated for its ability to improve fitness prior to liver resection for colorectal cancer with liver metastases. Thirty-eight patients (20 to rehabilitation, 18 to standard care) were randomized, and 35 (25 men and 10 women) completed both preoperative examinations and were analyzed. The median age was 62 (54-69) years, and there were no differences in baseline characteristics between the two groups. Rehabilitation resulted in improvements in preoperative oxygen consumption at the anaerobic threshold and maximum exercise capacity.

The effectiveness of moderate-intensity exercise on physical fitness, body composition and risk was tested by Román *et al.*[45] The patients were randomly divided into an exercise group (N.=14) and a group that completed a relaxation program (N.=9). In the interventional exercise group, an improvement was found according to cardiopulmonary exercise in total effort time (P<0.001) and anaerobic threshold ventilation time (anaerobic threshold time) (P=0.009). Dual energy X-ray absorptiometry showed a decrease in fat (P=0.003) and an increase in muscle mass (P=0.01), lean appendicular mass (P=0.03) and lean leg mass (P=0.02). The Timed Up&Go test decreased at the end of the study compared to baseline (P=0.02).

The benefit of exercise was also found in a meta-analysis by Williams *et al.*[15] An improvement was observed in the VO_{2peak}, the anaerobic threshold, the 6-minute Walk Test, muscle mass/function and quality of life. The most significant benefit was achieved with a combination of aerobic and strength training. Seven studies reported a predominant benefit with supervised exercise.

Limitations of the study

The current study has some limitations, including the low total number of patients after follow-up. The low level of patient compliance was the main limiting factor that prevented us from publishing the main conclusion about the benefit of the prehabilitation program compared with the standard of care. The low number of patients after the first follow-up can lead to a bias in the main result of the study. However, if the main problem in patients with liver cirrhosis is low adherence, then it is important to solve the problem and identify the barriers that are associated with the patient's refusal to cooperate with the medical staff.

Another limitation of the study is that it was applied in only one center, and it is assumed that a multicenter study would provide additional benefit on the issue.

Conclusions

Despite the great effort to maintain adherence, it is not possible to draw a conclusion about the effectiveness of prehabilitation in patients before liver transplantation compared with the standard of care because the main problem in Slovakian patients with liver cirrhosis is low adherence.

A promising result was found due to the improvement of the liver frailty index in the prehabilitation group and Child–Pugh score. More studies are needed to identify the barriers that lead to low adherence in patients with liver cirrhosis.

References

1. Jadlowiec CC, Taner T. Liver transplantation: current status and challenges. World J Gastroenterol 2016;22:4438–45.

2. Sepanlou SG, Safiri S, Bisignano C, *et al.*; GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020;5:245–66.

3. Casales da Silva Vieira R, Álvares-da-Silva MR, de Oliveira ÁR, da Silveira Gross J, Kruger RL, Dal Bosco A, *et al.* Cirrhosis affects maximal oxygen consumption, functional capacity, quality of life in patients with hepatitis C. Physiother Res Int 2018;23:e1727.

4. Ardeljan AD, Hurezeanu R. Sarcopenia. Treasure Island (FL): StatPearls Publishing; 2022.

5. Dhillon RJ, Hasni S. Pathogenesis and Management of Sarcopenia. Clin Geriatr Med 2017;33:17–26.

6. Larsson L, Degens H, Li M, Salviati L, Lee YI, Thompson W, *et al.* Sarcopenia: Aging-Related Loss of Muscle Mass and Function. Physiol Rev 2019;99:427–511.

7. Nishikawa H, Fukunishi S, Asai A, Nishiguchi S, Higuchi K. Sarcopenia and Frailty in Liver Cirrhosis. Life (Basel) 2021;11:399.

8. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, *et al.*; European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39:412–23.

9. Hanai T, Shiraki M, Nishimura K, Ohnishi S, Imai K, Suetsugu A, *et al.* Sarcopenia impairs prognosis of patients with liver cirrhosis. Nutrition 2015;31:193–9.

10. Montano-Loza AJ. Clinical relevance of sarcopenia in patients with cirrhosis. World J Gastroenterol 2014;20:8061–71.

11. Locklear CT, Golabi P, Gerber L, Younossi ZM. Exercise as an intervention for patients with end-stage liver disease: systematic review. Medicine (Baltimore) 2018;97:e12774.

12. Bellar A, Welch N, Dasarathy S. Exercise and physical activity in cirrhosis: opportunities or perils. J Appl Physiol 2020;128:1547–67.

13. Kalaitzakis E. Quality of Life in Liver Cirrhosis. In: Preedy VR, Watson RR, editors. Handbook of Disease Burdens and Quality of Life Measures. Springer; 2010. p. 2239-54.

14. Tandon P, Montano-Loza AJ, Lai JC, Dasarathy S, Merli M. Sarcopenia and frailty in decompensated cirrhosis. J Hepatol 2021;75(Suppl 1):S147–62.

15. Williams FR, Milliken D, Lai JC, Armstrong MJ. Assessment of the Frail Patient With End-Stage Liver Disease: A Practical Overview of Sarcopenia, Physical Function, and Disability. Hepatol Commun 2021;5:923–37.

16. Allison R 2nd, Assadzandi S, Adelman M. Frailty: evaluation and Management. Am Fam Physician 2021;103:219–26.

17. Proietti M, Cesari M. Frailty: What Is It? Adv Exp Med Biol 2020;1216:1–7.

18. Sieber CC. Frailty - From concept to clinical practice. Exp Gerontol 2017;87(Pt B):160–7.

19. Yeolekar ME, Sukumaran S. Frailty Syndrome: A Review. J Assoc Physicians India 2014;62:34–8.

20. Jetten WD, Hogenbirk RN, Van Meeteren NL, Cuperus FJ, Klaase JM, De Jong R. Physical Effects, Safety and Feasibility of Prehabilitation in Patients Awaiting Orthotopic Liver Transplantation, a Systematic Review. Transpl Int 2022;35:10330.

21. Hao S, Reis HL, Quinn AW, Snyder RA, Parikh AA. Prehabilitation for Older Adults Undergoing Liver Resection: Getting Patients and Surgeons Up to Speed. J Am Med Dir Assoc 2022;23:547–54.

22. Lambert JE, Hayes LD, Keegan TJ, Subar DA, Gaffney CJ. The Impact of Prehabilitation on Patient Outcomes in Hepatobiliary, Colorectal, and Upper Gastrointestinal Cancer Surgery: A PRISMA-Accordant Meta-analysis. Ann Surg 2021;274:70–7. [d]

23. 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;69:1164–77.

24. Tavabie O, McKie P, Webzell I, *et al.* Anxiety and depression on the liver transplant waiting list: a case for psychological prehabilitation? Gastrointest Nurs 2020;18(Suppl. 6):S22–7.

25. Debette-Gratien M, Tabouret T, Antonini MT, Dalmay F, Carrier P, Legros R, *et al.* Personalized adapted physical activity before liver transplantation: acceptability and results. Transplantation 2015;99:145–50.

26. Brustia R, Monsel A, Skurzak S, Schiffer E, Carrier FM, Patrono D, *et al.* Guidelines for Perioperative Care for Liver Transplantation: Enhanced Recovery After Surgery (ERAS) Recommendations. Transplantation 2022;106:552–61.

27. Vinaixa C, Martínez Palli G, Milliken D, Sellers D, Dharancy S, Spiro M, *et al.*; ERAS4OLT.org Working Group. The role of prehabilitation on short-term outcomes after liver transplantation: A review of the literature and expert panel recommendations. Clin Transplant 2022;36:e14686.

28. Armstrong MJ, Williams FR. Prehabilitation and General Management. In: Liver Transplantation. John Wiley & Sons, Ltd; 2021. p. 116-22.

29. Kamath PS, Kim WR; Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). Hepatology 2007;45:797–805.

30. Kim WR, Mannalithara A, Heimbach JK, Kamath PS, Asrani SK, Biggins SW, *et al.* MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era. Gastroenterology 2021;161:1887–1895.e4.

31. Tsoris A, Marlar CA. Use Of The Child Pugh Score In Liver Disease. Treasure Island (FL): StatPearls Publishing; 2022.

32. Wang CW, Lebsack A, Chau S, Lai JC. The Range and Reproducibility of the Liver Frailty Index. Liver Transpl 2019;25:841–7.

33. Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, *et al.* Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology 2017;66:564–74.

34. Balestroni G, Bertolotti G. [EuroQol-5D (EQ-5D): an instrument for measuring quality of life]. Monaldi Arch Chest Dis 2012;78:155–9.

35. König HH, Ulshöfer A, Gregor M, von Tirpitz C, Reinshagen M, Adler G, *et al.* Validation of the EuroQol questionnaire in patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol 2002;14:1205–15.

36. Tajima R, Kondo M, Kai H, Saito C, Okada M, Takahashi H, *et al.*

Measurement of health-related quality of life in patients with chronic kidney disease in Japan with EuroQol (EQ-5D). Clin Exp Nephrol 2010;14:340–8.

37. Ragusa R, Bertino G, Bruno A, Frazzetto E, Cicciu F, Giorgianni G, *et al*. Evaluation of health status in patients with hepatitis c treated with and without interferon. Health Qual Life Outcomes 2018;16:17.

38. Skladany L, Vnencakova J, Laffers L, Skvarkova B, Hrubá E, Molcan P, *et al.* Adherence to Oral Nutritional Supplements After Being Discharged from the Hospital is Low but Improves Outcome in Patients with Advanced Chronic Liver Disease. Patient Prefer Adherence 2021;14:2559–72.

39. Kok B, Whitlock R, Ferguson T, James Bailey R, Warren Burak K, Kowalczewski J, *et al.* Health-Related Quality of Life: A Rapid Predictor of Hospitalization in Patients With Cirrhosis. Am J Gastroenterol 2020;115:575–83.

40. 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.

41. Duarte-Rojo A, Ruiz-Margáin A, Montaño-Loza AJ, Macías-Rodríguez RU, Ferrando A, Kim WR. Exercise and physical activity for patients with end-stage liver disease: improving functional status and sarcopenia while on the transplant waiting list. Liver Transpl 2018;24:122–39.

42. Lemyze M, Dharancy S, Wallaert B. Response to exercise in patients with liver cirrhosis: implications for liver transplantation. Dig Liver Dis 2013;45:362–6.

43. Lai JC, Dodge JL, Kappus MR, Wong R, Mohamad Y, Segev DL, *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;116:717–22.

44. Dunne DF, Jack S, Jones RP, Jones L, Lythgoe DT, Malik HZ, *et al.* Randomized clinical trial of prehabilitation before planned liver resection. Br J Surg 2016;103:504–12.

45. 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;59:1966–75.

Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding
This study was supported with an internal grant from the Slovak Medical University (grant n. 05/2022-SVG1).

Authors' contributions
Ľubomír Skladaný and Tomáš Koller: conceptualization. Ľubomír Skladaný, Tomáš Koller, and Daniel Gurín: methodology. Ľubomír Skladaný and Janka Vnenčáková: validation and supervision. Daniel Gurín, Dávid Líška, and Tomáš Koller: formal analysis. Roman Bednár, Ľubomír Skladaný, and Pavol Molčan: investigation. Ľubomír Skladaný and Dávid Líška: writing. Ľubomír Skladaný and Dávid Líška: original draft preparation. Ľubomír Skladaný, Dávid Líška, Daniel Gurín, Pavol Molčan, Roman Bednár: writing—review and editing. Janka Vnenčáková and Tomáš Koller: project administration. All authors contributed to the article and approved the submitted version.

History
Article first published online: December 7, 2023. - Manuscript accepted: November 3, 2023. - Manuscript revised: October 11, 2023. - Manuscript received: July 10, 2023.

Supplementary data
For supplementary materials, please see the HTML version of this article at www.minervamedica.it