Multimodal prehabilitation before liver transplantation: a randomized controlled study of aerobic exercise, resistance training, and electromyostimulation

Abstract

Background: Patients awaiting liver transplantation frequently experience progressive frailty, sarcopenia, reduced physical performance, and deterioration in functional capacity, all of which negatively influence clinical outcomes and prognosis. Multimodal prehabilitation combining exercise interventions and nutritional support may represent an effective strategy to optimize physical condition before transplantation. The aim of this study was to evaluate the effectiveness of aerobic exercise, resistance training, electromyostimulation (EMS), and nutritional support in patients with liver cirrhosis awaiting liver transplantation.

Methods: 96 patients were randomized. Eleven patients were lost to follow-up, resulting in a final analysis of 85 participants with liver cirrhosis recruited from the RH7 registry. Participants were randomized into either a multimodal prehabilitation group (n = 42) or a standard-of-care (SOC) group (n = 43). The intervention consisted of a individualized prehabilitation program including aerobic cycle ergometry, resistance training using elastic bands or body-weight exercises, EMS focused on the quadriceps femoris muscle, and nutritional support. Frailty status was assessed using the Liver Frailty Index (LFI). Liver disease severity was evaluated using the MELD and Child–Pugh scores.

Results: The intervention group demonstrated a significant improvement in frailty status after the prehabilitation program. Mean LFI decreased from 4.60 ± 0.82 at baseline to 4.51 ± 0.88 after intervention ($p = 0.05$). In contrast, the SOC group demonstrated worsening frailty, with mean LFI increasing from 4.45 ± 0.98 to 4.67 ± 0.98 ($p = 0.04$). Between-group comparison after intervention did not demonstrate statistically significant differences ($p = 0.2$). The Child–Pugh score decreased in the intervention group from 9.51 ± 2.28 to 8.74 ± 2.19, although this change did not reach statistical significance ($p = 0.08$). Similarly, no significant change was observed in the standard care group (from 9.95 ± 2.23 to 9.66 ± 2.24, $p = 0.07$). There was no significant difference between the groups ($p = 0.78$). A significant improvement was observed for the MELD score in the intervention group, which decreased from 22.00 ± 7.17 to 19.08 ± 7.32 ($p = 0.02$). No significant change occurred in the standard care group (from 23.67 ± 8.11 to 23.70 ± 8.43, $p = 0.48$). Moreover, the between-group comparison demonstrated a statistically significant difference in MELD score changes in favor of the intervention group ($p = 0.04$).

Conclusion: Multimodal prehabilitation consisting of aerobic exercise, resistance training,

EMS, and nutritional support may positively influence patients' status in patients with liver cirrhosis awaiting liver transplantation. The findings support the implementation of structured multidisciplinary prehabilitation strategies in hepatology and liver transplantation care, particularly for frail patients with limited exercise tolerance.
Further randomized controlled studies with larger cohorts and long-term follow-up are needed to confirm the long-term clinical benefits of this intervention.

Keywords: liver transplantation, prehabilitation, liver frailty index, cirrhosis, sarcopenia, electromyostimulation, rehabilitation

Introduction

Chronic liver diseases and end-stage liver cirrhosis represent a significant global health problem associated with high morbidity, mortality, and a substantial reduction in patients' quality of life (1–3). Liver transplantation is currently considered the most effective treatment option for patients with end-stage liver failure; however, the waiting period for transplantation is often accompanied by a progressive decline in physical performance, muscle mass, functional capacity, and overall health status (4–6). Patients awaiting liver transplantation frequently experience complications such as sarcopenia, frailty syndrome, fatigue, reduced aerobic capacity, and mobility impairments, all of which significantly affect prognosis, hospitalization risk, and postoperative outcomes (7–10).

Sarcopenia and frailty are among the most important prognostic factors of mortality in patients with liver cirrhosis (11). The etiology of muscle wasting in patients with liver disease is multifactorial and includes chronic inflammation, malnutrition, hormonal alterations, hypermetabolism, physical inactivity, and impaired skeletal muscle regeneration (12–15). For these reasons, increasing attention has recently been directed toward the implementation of prehabilitation interventions in the management of patients prior to liver transplantation (16–18). Prehabilitation represents a multidisciplinary approach aimed at optimizing the patient's physical and psychological condition before a planned medical intervention in order to increase physiological reserve and improve postoperative outcomes (19–21). In the field of liver transplantation, rehabilitation primarily focuses on improving cardiorespiratory fitness, muscle strength, functional performance, mobility, and quality of life. Aerobic exercise, resistance training, and, more recently, electromyostimulation constitute important components of prehabilitation programs. Aerobic exercise has been associated with improvements in cardiorespiratory fitness, exercise tolerance, peripheral circulation, and reduction of fatigue . In patients with liver disease, regular aerobic training may positively influence maximal oxygen

uptake, functional capacity, and metabolic parameters (22–24). Resistance training is particularly important in the prevention and management of sarcopenia, as it promotes the preservation or increase of muscle mass and muscle strength (25,26). Therefore, the combination of aerobic and resistance exercise appears to be a promising strategy for optimizing the physical condition of patients awaiting liver transplantation. In recent years, electromyostimulation has also gained increasing attention as an alternative or complementary method of muscle activation through electrical impulses. Electromyostimulation may be particularly beneficial for patients with severe physical weakness, low exercise tolerance, or limited ability to perform conventional exercise interventions (27,28) . Despite growing interest in this intervention, there remains a lack of high-quality studies evaluating the effectiveness of electromyostimulation in patients awaiting liver transplantation. In the previous study, we tested the effectiveness of prehabilitation compared to standard care. In this study, we supplemented the therapeutic program with electromyostimulation. The aim of this study is to evaluate the effectiveness of aerobic exercise, resistance training, and electromyostimulation with nutrition support as components of prehabilitation in patients awaiting liver transplantation.

Materials and methods

This was a prospective, randomized, two-arm study registered under ClinicalTrials.gov (NCT04767945). Patients were recruited from the RH7 registry, which includes adult hospitalized patients with ACLD/dACLD in Slovakia. The RH7 registry was established in 2014 at the Department of Hepatology, Gastroenterology and Transplantation, II. Internal Clinic of the Slovak Medical University (HEGITO).

All participants had to provide written informed consent before enrolment. Only active patients registered in RH7 were included. Patients who refused to sign informed consent were excluded. Additional exclusion criteria included coma, severe hepatic encephalopathy, fever, acute injury, post-traumatic conditions associated with functional deficits, peripheral or central paresis, and recent stroke. After hospitalization and confirmation of eligibility, patients were randomized into either the active prehabilitation group or the standard of care (SOC) group.

Randomization was performed using dedicated software, and group allocation was concealed and managed by an administrative worker. Following enrolment, demographic, clinical, anthropometric, and laboratory data were collected to assess the etiology and severity of ACLD, as well as nutritional status, sarcopenia, and frailty.

The sample

The participants consisted of 85 patients with liver cirrhosis (55 men and 30 women). The study participants were divided into a prehabilitation group (n = 42; 26 men and 16 women) and a standard-of-care group (n = 43; 29 men and 14 women). Baseline characteristics of the study population are presented in Table 1. The flow diagram of the study is shown in Figure 1.

Table 1 Baseline characteristics of the whole group

	Prehab group (n = 42)	**Standard of care group (n = 43)**	**All (n = 85)**	**p**
Gender (F)	16	14	30	
Age	55.55 ± 12.09	56 ± 11,94	55.66 ± 11.99	0.43
Height	173.23 ± 9.27	173.44 ± 8,60	173.21 ± 8.84	0.49
Weight	78.02 ± 17.87	85.74 ± 19.76	81.05 ± 17.10	0.11
BMI	25.90 ± 5.06	27.1 ± 5.95	26.68 ± 4.98	0.13
MELD	22 ± 7.17	23.67 ± 8.11	22.84 ± 7.66	0.12
CPS	9.51 ± 2.28	9.95 ± 2.23	9.58 ± 2.20	0.14
LFI	4.60 ± 0.82	4.45 ± 0.98	4.52 ± 0.90	0.15
Aetiology of cirrhosis				
ALD, n/%	29 (69%)	32 (74.4%)	61 (71.8%)	
other, n/% (NASH, HBC, HCV, PBC, PSC)	13 (31%)	11 (25.6%)	24 (28.2%)	

F – female, BMI – body mass index, MELD – The Model for the End-Stage Liver Disease, CPS – 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

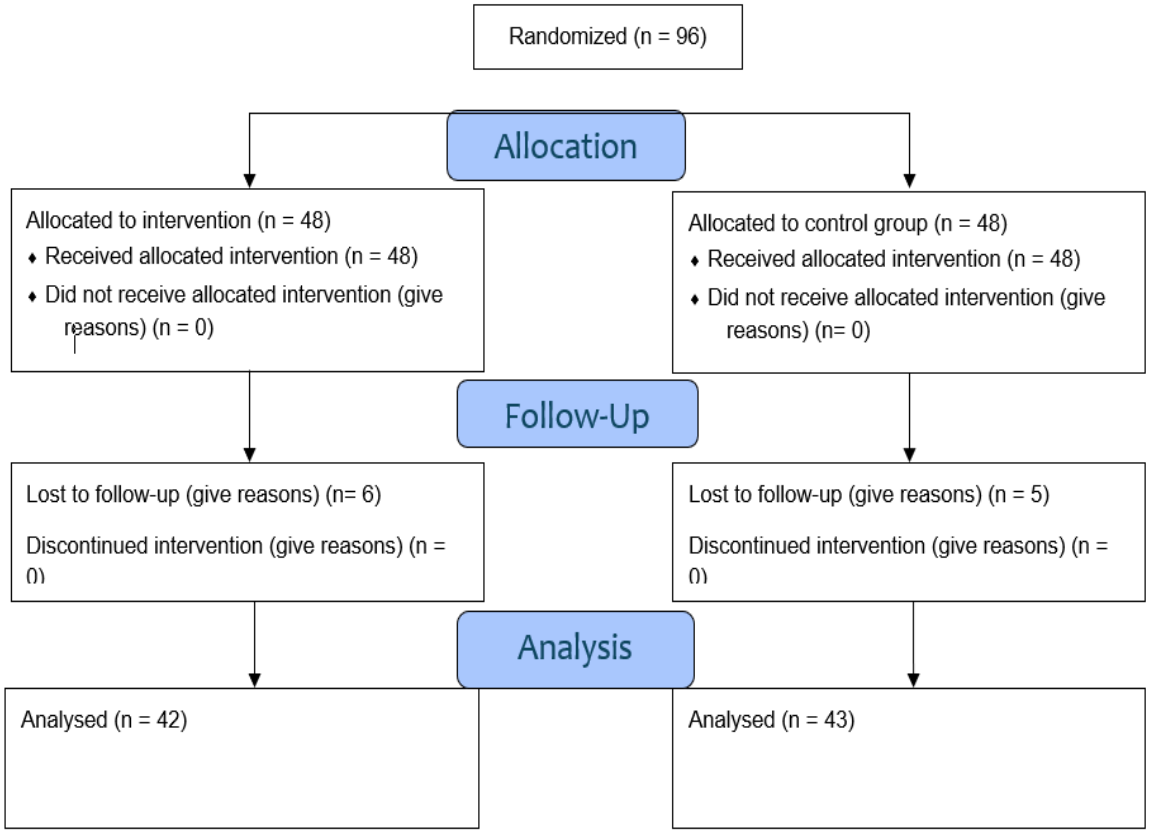

Figure 1 Flow diagram

Liver frailty index (LFI)

LFI was used to assess frailty syndrome. The LFI is a standardized and validated tool specifically designed for patients with chronic liver disease and cirrhosis (29). It enables an objective evaluation of physical performance and frailty status through simple functional tests focused on muscle strength, balance, and mobility . Currently, the LFI is considered one of the most important functional prognostic indicators in patients with liver disease, as higher scores are associated with an increased risk of hospitalization, complications, mortality, and poorer liver transplantation outcomes (30–33).

The LFI assessment consisted of three functional tests: handgrip strength measurement using a handheld dynamometer, the chair stand test, and static balance testing in three positions. Handgrip strength was measured on the dominant upper limb, and the best value from repeated attempts was recorded. The chair stand test evaluated the time required to complete five repeated sit-to-stand movements without the use of the upper limbs. Balance assessment was performed in three standardized standing positions maintained for a defined period of time. Based on the obtained data, the total LFI score was subsequently calculated using the standardized algorithm. Higher scores indicated a greater degree of frailty and lower physical performance of the patient.

MELD

The Model for End-Stage Liver Disease (MELD) score was used to assess the severity of liver disease and predict short-term mortality risk in patients with chronic liver disease and cirrhosis (34). The MELD score is a widely used and validated prognostic tool originally developed for patients undergoing transjugular intrahepatic portosystemic shunt procedures and is currently routinely utilized in clinical hepatology and liver transplantation programs worldwide (35,36). Higher MELD scores indicate more severe liver dysfunction and are associated with an increased risk of mortality and liver-related complications (37).

The MELD score was calculated using routinely obtained laboratory parameters, including serum bilirubin, serum creatinine, and the international normalized ratio (INR). Laboratory values were obtained as part of routine clinical examination and recorded from the patients' medical documentation.

Child-Pugh score

The Child–Pugh score was used to assess the severity and prognosis of chronic liver disease and cirrhosis. The Child–Pugh classification is a standardized and widely used clinical scoring

system that evaluates liver function and predicts disease progression, complications, and mortality risk in patients with chronic liver disease. The score allows categorization of patients into different stages of hepatic impairment and is commonly utilized in hepatology and liver transplantation practice (38–40). The Child–Pugh score was determined based on five clinical and biochemical parameters: serum bilirubin, serum albumin, international normalized ratio (INR) or prothrombin time, presence and severity of ascites, and degree of hepatic encephalopathy. Each parameter was assigned a score ranging from 1 to 3 points according to the severity of impairment, with the total score subsequently classifying patients into Child–Pugh class A, B, or C. Child–Pugh class A represented compensated liver disease with the best prognosis, whereas classes B and C indicated progressively more severe hepatic dysfunction and poorer prognosis. Clinical and laboratory data necessary for score calculation were obtained from routine medical examinations and patient medical records.

Prehabilitation (intervention group)

The proposed rehabilitation protocol was designed as a multimodal prehabilitation intervention for patients with liver cirrhosis. The program was implemented during hospitalization over a period of 2.5 weeks, with the frequency of training sessions set at a minimum of three or more therapy sessions per week. The overall structure of the intervention was strictly individualized and continuously monitored according to the patient's clinical condition. Prior to each training session, target training zone 1 was determined for each patient. This low-intensity zone (approximately 50–60% of maximal heart rate) was selected regarding patient safety. The initial phase of the training consisted of cycle ergometry lasting 10–20 minutes. The use of a cycle ergometer was chosen to ensure controlled load dosing and to minimize the risk of falls in frail patients. The aim of this phase was to improve cardiovascular fitness and stimulate aerobic metabolism. The subsequent phase consisted of resistance training performed in the form of strengthening exercises lasting 10–15 minutes. Due to the degree of fatigue and limited mobility in some patients, the exercises were performed in bed positions (supine, semi-seated, or standing positions). The intervention focused on the activation of large muscle groups of the lower and upper extremities using elastic resistance bands (thera-band) or body weight exercises. Electromyostimulation (EMS) constituted the final part of the protocol and lasted 15–25 minutes. EMS was used as an adjunctive method to facilitate muscle hypertrophy and prevent muscle atrophy in patients. The stimulation primarily targeted the quadriceps femoris muscle, which is essential for postural stability and locomotion. The stimulation parameters were adjusted to induce a visible but non-painful muscle contraction (Table 2).

Table 2 Intervention according to TIDIER Checklist

Name of the intervention	Multimodal prehabilitation combining aerobic training, strength training, nutritional support and electromyostimulation (EMS).
Why	The main objective was to verify the effectiveness of prehabilitation during hospitalization in patients with liver cirrhosis,
Materials	As part of the therapy, we used a stationary bike, elastic resistance bands, an EMS device with surface electrodes, and diagnostic tools: a stopwatch, pulse oximeter, and blood pressure monitor.
Intervention	Aerobic phase: 10-20 minutes of cycling in training zone 1 (low intensity). Strength phase: 10-15 minutes of resistance training on a bed targeting large muscle groups. Stimulation phase: 15-25 minutes of EMS application to the lower extremities.
Who provides the intervention	The entire process took place under the direct supervision and guidance of a physiotherapist.
How the intervention is delivered	An individual form of intervention is carried out directly at the patient's bedside or in the ward.
Place	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;
When and how much	The intervention took place during a 2.5-week hospitalization with a frequency of at least 5 times a week.
Individualization	The training plan was individually modified based on the patient's current condition and subjective tolerance to stress.
Modification	An individual form of intervention carried out directly at the patient's bedside or in the ward.

Planned adherence	Each completed training unit was recorded in a protocol, and the continuity of exercise was monitored throughout the entire length of hospitalization.

Standard of care (control group)

Standard care (SOC) for patients awaiting liver transplantation consisted of a structured 30-minute educational interview focused on lifestyle modification, physical activity, and nutritional management. Patients received recommendations regarding healthy lifestyle habits and regular exercise participation. Nutritional counseling emphasized maintaining meal intervals of approximately 3–4 hours, including the incorporation of a late evening snack. Patients were provided with two bottles of Nutridrink daily. Oral nutritional supplementation in the form of sipping was intended to complement regular dietary intake and improve adherence to recommended nutritional intervals. Nutritional education also included guidance on appropriate food choices with a particular emphasis on adequate protein consumption. Regarding physical activity, patients received both verbal and written instructions highlighting the importance of regular exercise, maintenance of muscle mass and strength, prevention of sarcopenia, and the potential therapeutic benefits of physical activity. In addition to oral counseling, patients were provided with a list of safe exercises. They were encouraged to perform physical activity for approximately 15–20 minutes at least three times per week.

Statistical analysis

All baseline demographic and clinical characteristics were systematically recorded using Microsoft Excel 2016®. Statistical analyses were subsequently performed in IBM SPSS Statistics®. Descriptive statistical methods were applied to characterize the study sample and summarize the obtained data. The distribution normality of continuous variables was assessed using the Shapiro–Wilk test. Depending on the results of the normality assessment, parametric or non-parametric statistical procedures were selected. Differences within groups were evaluated using the paired t-test for normally distributed variables and the Wilcoxon signed-rank test for non-normally distributed data. Comparisons between groups were performed using the independent-samples t-test or the Mann–Whitney U test, as appropriate. Categorical variables, including mortality, were compared using Fisher's exact test. The effect of the intervention on 90-day mortality was expressed as relative risk (RR), odds ratio (OR), absolute

risk reduction (ARR), and number needed to treat (NNT), all with corresponding 95% confidence intervals. Statistical significance was set at $p < 0.05$.

Results

Ninety-six patients were randomized. Eleven patients were lost to follow-up, resulting in a final analysis of 85 participants. The analysis of LFI demonstrated a significant improvement in frailty status in the intervention group following the multimodal prehabilitation program. In the prehabilitation group, the mean LFI value decreased from 4.60 ± 0.82 at baseline to 4.51 ± 0.88 after the intervention, indicating an improvement in physical performance and a reduction in frailty severity. This change reached statistical significance ($p = 0.05$). In contrast, the SOC group showed a worsening tendency in frailty status, with the mean LFI increasing from 4.45 ± 0.98 at baseline to 4.67 ± 0.98 after the observation period. Although a statistically significant within-group difference was also observed ($p = 0.04$), the direction of change suggested deterioration of functional status in patients who received only standard care. Comparison between groups after intervention demonstrated no statistically significant differences in LFI values ($p = 0.2$).

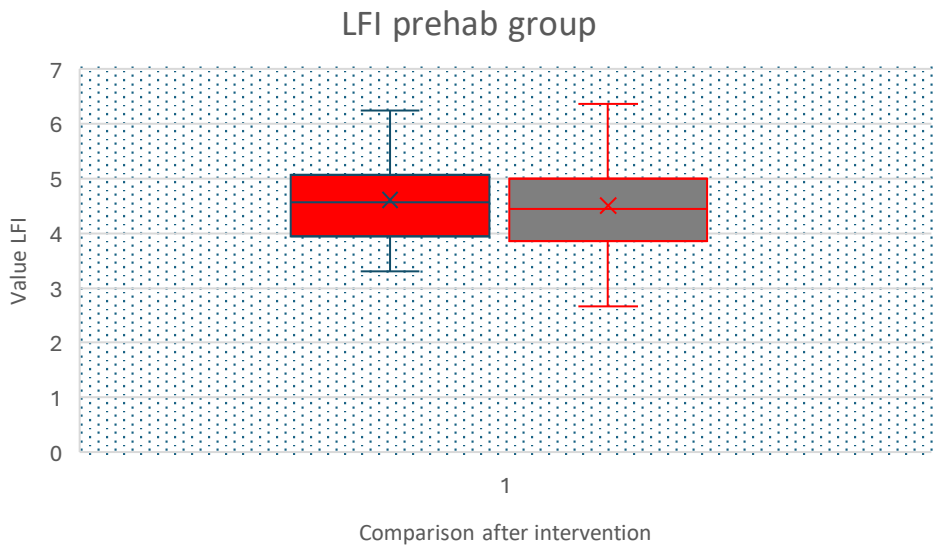

Figure 2. Comparison of liver frailty index in the prehabilitation group

Table 3 Outcomes of patients in the prehab study

	Period	Intervention group Mean ± SD	p	Standard of care Mean ± SD	p	Between groups p
LFI	Baseline	4.60 ± 0.82	**0.05**	4.45 ± 0.98	0.04	0.2
	After	4.51 ± 0.88		4.67 ± 0.98		
CPS	Baseline	9.51 ± 2.28	0.08	9.95 ± 2.23	0.07	0.78
	After	8.74 ± 2.19		9.66 ± 2.24		
MELD	Baseline	22 ± 7.17	**0.02**	23.67 ± 8.11	0.48	**0.04**
	After	19.08 ± 7.32		23.70 ± 8.43		

MELD – Model for End-Stage Liver Disease, CPS – Child-Pugh score, LFI – liver frailty index

Table 3 summarizes the changes in liver LFI, Child–Pugh score and MELD score before and after the intervention in the prehabilitation and standard care groups. The Child–Pugh score decreased in the intervention group from 9.51 ± 2.28 to 8.74 ± 2.19, although this change did not reach statistical significance (p = 0.08). Similarly, no significant change was observed in the standard care group (from 9.95 ± 2.23 to 9.66 ± 2.24, p = 0.07). There was no significant difference between the groups (p = 0.78). A significant improvement was observed for the MELD score in the intervention group, which decreased from 22.00 ± 7.17 to 19.08 ± 7.32 (p = 0.02). No significant change occurred in the standard care group (from 23.67 ± 8.11 to 23.70 ± 8.43, p = 0.48). Moreover, the between-group comparison demonstrated a statistically significant difference in MELD score changes in favor of the intervention group (p = 0.04).

90 days mortality

Ninety-day mortality was 19.0% in the prehabilitation group and 33.3% in the control group. Although mortality was numerically lower in the prehabilitation group, the difference did not

reach statistical significance (Fisher's exact test, $p = 0.205$). The relative risk of death was 0.57 (95% CI 0.27–1.23), and the odds ratio was 0.47 (95% CI 0.17–1.30). The absolute risk reduction was 14.3%, corresponding to a number needed to treat (NNT) of 7.

Patients in the prehabilitation group had an approximately 43% lower relative risk of 90-day mortality. The odds of death were approximately 53% lower in the prehabilitation group; however, this difference did not reach statistical significance. Prehabilitation was associated with an absolute reduction in 90-day mortality of 14.3 percentage points. Based on the calculated number needed to treat (NNT), approximately seven patients would need to undergo the prehabilitation program to prevent one death within 90 days.

Discussion

The present randomized controlled study evaluated the effectiveness of a multimodal prehabilitation program consisting of aerobic exercise, resistance training, EMS, and nutritional support in patients with liver cirrhosis awaiting liver transplantation. The main finding of this study was that patients who participated in the multimodal intervention demonstrated a significant improvement in frailty status, as reflected by a reduction in LFI values following the intervention. In contrast, patients receiving standard care showed a deterioration in frailty status during the observation period. These findings support the growing evidence that structured prehabilitation may positively influence physical performance and functional reserve in patients with advanced chronic liver disease.

Frailty and sarcopenia are increasingly recognized as major prognostic factors in liver cirrhosis and liver transplantation . Previous studies demonstrated that impaired muscle strength, reduced mobility, and decreased physical performance are associated with increased mortality, prolonged hospitalization, higher complication rates, and poorer transplantation outcomes (41–47). The Liver Frailty Index has become one of the most widely used functional assessment tools in hepatology due to its ability to objectively evaluate frailty through functional performance testing (48). In the present study, the baseline LFI values indicated a clinically relevant degree of frailty in both groups, confirming the severe functional impairment commonly observed in patients with decompensated cirrhosis.

The observed improvement in LFI in the intervention group suggests that even a relatively short-term multimodal intervention performed during hospitalization may positively influence functional status in this vulnerable population. Although the absolute reduction in LFI was modest, previous evidence indicates that even small changes in frailty status may have important prognostic implications in cirrhotic patients. Lai et al. (49) demonstrated that

dynamic changes in frailty are associated with waitlist mortality and clinical outcomes in patients awaiting liver transplantation. Therefore, stabilization or improvement of physical performance may represent an important therapeutic target in pre-transplant care.

The deterioration observed in the standard-of-care group is also clinically important. Patients with advanced liver disease frequently experience progressive declines in muscle mass and functional capacity due to chronic inflammation, hypermetabolism, malnutrition, hormonal dysregulation, and physical inactivity (50–53). Without structured exercise intervention, hospitalization itself may further accelerate physical deconditioning and functional decline. The worsening tendency observed in the control group in our study supports the hypothesis that standard educational counseling alone may be insufficient to prevent deterioration of frailty during hospitalization.

A unique aspect of the present study was the incorporation of electromyostimulation into the multimodal prehabilitation protocol. EMS has recently gained attention as a potential adjunctive therapy in sarcopenic and frail populations due to its ability to stimulate muscle activation even in individuals with limited voluntary exercise capacity (54–56). In patients with advanced cirrhosis, severe fatigue, weakness, and reduced exercise tolerance may substantially limit participation in conventional exercise programs. EMS may therefore represent a particularly suitable complementary intervention in this clinical setting. The stimulation protocol in our study primarily targeted the quadriceps femoris muscle, which plays a crucial role in mobility, balance, and postural stability. Although previous studies investigated EMS in sarcopenic populations, evidence in liver transplantation candidates remains limited. Our findings suggest that EMS may be feasibly integrated into multidisciplinary prehabilitation protocols during hospitalization. However, because the intervention combined aerobic exercise, resistance training, EMS, and nutritional support simultaneously, the isolated contribution of EMS to the observed improvement cannot be definitively determined. Future studies should therefore investigate the independent effects of EMS and compare multimodal versus exercise-only interventions.

Several limitations of this study should be acknowledged. First, the intervention duration was short and restricted to hospitalization. Longer-term follow-up was not available; therefore, the sustainability of observed improvements remains unclear. Second, the intervention combined multiple therapeutic components simultaneously, making it difficult to determine the individual contribution of aerobic exercise, resistance training, EMS, and nutritional support. Finally, the study primarily focused on frailty outcomes and did not muscle mass quantification, aerobic performance parameters, transplantation outcomes, or long-term survival. Despite these

limitations, the study provides important preliminary evidence supporting the implementation of multimodal prehabilitation in patients awaiting liver transplantation. The intervention was feasible, individualized, and associated with improved frailty status during hospitalization. Future randomized controlled studies with larger cohorts, longer intervention periods, and long-term postoperative follow-up are needed to further clarify the effectiveness of multimodal prehabilitation and the specific role of electromyostimulation in patients with advanced liver disease.

Conclusion

The present randomized controlled study demonstrated that multimodal prehabilitation consisting of aerobic exercise, resistance training, electromyostimulation, and nutritional support may positively influence patients status in patients with liver cirrhosis awaiting liver transplantation. Patients participating in the intervention showed significant improvement, whereas patients receiving standard care demonstrated deterioration in functional status during hospitalization. These findings suggest that structured and individualized prehabilitation may represent a feasible and clinically beneficial strategy for optimizing physical performance and physiological reserve in this vulnerable patient population.

The integration of electromyostimulation into the rehabilitation protocol appears to be a promising complementary approach, particularly for frail patients with limited exercise tolerance and severe muscle weakness. Although the isolated contribution of EMS could not be determined, the overall intervention was safe, feasible, and well tolerated during hospitalization.

Despite the encouraging findings, additional randomized controlled studies with larger sample sizes, longer intervention duration, and postoperative follow-up are necessary to further clarify the long-term effects of multimodal prehabilitation and its impact on transplantation outcomes, hospitalization, quality of life, and survival.

Conflict of interest

Authors declare no conflict of interest

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