Exercise Training for Liver Transplant Candidates

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ABSTRACT

Background and Aims. Frailty is associated with increased morbidity and mortality, and this is tightly linked to liver decompensation and increased complication rates among liver transplant (LT) candidates. The aim of the study was to evaluate the efficacy of a structured in- and outpatient exercise training program for cirrhotic patients who were referred for liver transplant evaluation.

Methods. We retrospectively reviewed 458 consecutive LT patients. There were 200 patients who underwent LT prior to the implementation of an exercise training program (non-ETP) and 258 LT patients who underwent a comprehensive exercise training program (ETP).
Baseline characteristics, readmission rate, and length of hospital stay (LOS) were analyzed and compared between the 2 groups.

Results. The ETP group were more likely to have diabetes mellitus and coronary artery disease. However, there was no significant difference in the postoperative complication rates between the 2 groups except for more infections in the ETP group compared to the non-ETP group. There was a trend toward lower 90-day readmission rate in the ETP group (17.9% vs 20%) and shorter LOS (14 vs 17 days).

Conclusion. There was a trend toward reduced 90-day readmission and shorter length of stay after implementation of an exercise training program.

LIVER transplantation is a life-saving surgery for patients with chronic liver disease, acute liver failure, inherited metabolic diseases, and certain hepatic malignancies [1]. Since its advent in the 1960s, the field of liver transplantation has tremendously progressed with advances in surgical techniques, organ procurement and preservation, immunosuppressive therapy, and organ allocation [2]. Patients are rigorously assessed prior to transplant to determine if they are appropriate candidates for a major surgery. Now patients who otherwise might not survive without a liver transplant have a post-transplant 5-year survival of 75% and an improved quality of life [3,4].

Tens of thousands of liver transplants are performed annually worldwide. Liver transplantation requires intensive resource utilization, which makes it quite expensive. In the United States, the mean hospital charges are $358,200, and the mean inpatient costs of liver transplantation are $114,300 [5]. Despite the substantial costs associated with liver transplantation, it remains a cost-effective procedure [6]. It is imperative, in a cost-sensitive era, to provide excellent care efficiently while minimizing cost. Organ shortage remains a major issue with liver transplantation. The model for end-stage liver disease-sodium (MELD-Na) is now widely used to prioritize patients most in need of liver

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0041-1345/19
https://doi.org/10.1016/j.transproceed.2019.08.045

transplantation and has led to a reduction in waitlist mortality; however, it remains an imperfect score and patients continue to die on the waitlist, in part as supply does not meet demand [7].

Hospital readmission is a useful marker of the quality of care within a health care system [8]. It is a predictor of higher resource utilization and cost. It is estimated that the cost of readmission in the United States may exceed $40 billion per year [9]. Due to the complexity of liver transplantation, the readmission rate is even higher among these patients [10,11]. The 30-day readmission rate has been reported to be as high as 41% to 45% [10,12]. Predictors of readmission in these studies included hepatitis C, hypoalbuminemia, diabetes, pretransplant portal vein thrombosis, pretransplant hospitalization within 90 days, elevated creatinine, postoperative complications, and below a college level education [9–11]. Several studies have determined that identifying risk factors for readmission and modifying them in patients with cirrhosis improved quality of care and resulted in a decrease in hospital readmission [13–16].

Physical frailty and sarcopenia have gained scientific attention in patients with cirrhosis due to their negative impacts on patients' survival and quality of life [17–19]. In addition, both entities are associated with longer hospitalization, longer intensive care unit stay, and higher readmission rate in the pre- and post-liver transplant setting [16,20,21]. Therefore, nutritional interventions with comprehensive physiotherapy programs may improve outcomes among liver transplant candidates. Williams et al launched a comprehensive rehabilitation program for patients on the liver transplant waitlist. The program resulted in improving 6-minute walking distance and patient satisfaction compared to the control group [22]. We launched a comprehensive in- and outpatient exercise training program for our transplant candidates in 2012. The goal of the program was to improve exercise tolerance and improve the frailty status of patients in the pretransplant setting. The purpose of this study was to evaluate the efficacy of a structured in- and outpatient exercise training program for cirrhotic patients who were referred for liver transplant evaluation.

STUDY DESIGN AND POPULATION

We conducted a retrospective cohort study consisting of consecutive patients who underwent a liver transplant between January 2006 and September 2016 at the Multi-Organ Transplant Unit at London Health Sciences Centre. Our center provides tertiary-level care to Southwestern Ontario with a catchment area of 1.5 million inhabitants and is affiliated with Western University (London, Ontario, Canada). Data was obtained from the transplant database, which is prospectively maintained and updated. All patients who underwent liver transplant were included. The only exclusion criteria were patients who did not survive the index hospitalization at the time of liver transplantation since they would not be at risk for the primary outcome, 90-day readmission. Approval for this study was obtained from the local Research Ethics Board prior to commencement of the study.

The cohort was divided into 2 groups: patients who were enrolled prior to the implementation of an exercise training program (non-ETP group) versus after its introduction (ETP group). Baseline variables were collected in both groups, including age, sex, type of liver disease, body mass index, comorbidities, serum albumin, and the biological sodium model for end-stage liver disease (MELD-Na) at the time of listing for liver transplantation. The length of hospitalization and intensive care unit stay before and after liver transplantation were also recorded. Donor information including donor age, gender, race, type of liver, allograft (brain dead or donation after cardiac death or living donor), cold ischemia time and warm ischemia time, and donor risk index were also obtained. Postoperative complications during the index hospitalization were also collected.

INTERVENTION

In 2012, the Multi-Organ Transplant Program began evaluating the functional status of transplant candidates as part of the overall assessment for transplant candidacy.

Subjective reports of Activities of Daily Living and Instrumental Activities of Daily Living were combined with objective measures of 6 minute-walk test (6MWT), hand-held dynamometry, and the Duke Activity Status Index (DASI) to provide an objective assessment of functional mobility.

The functional mobility findings were then communicated to the transplant team to be combined with traditional assessment findings for the team's decision regarding eligibility. Successful candidates were listed immediately. Some however, required that the decision for listing be deferred pending improved exercise conditioning, while others were determined to be non-liver transplant candidates due to a high probability of poor outcomes.

Patients who had acceptable functional mobility (6MWT $>$ 250 m, grip strength $>$ 30 kg man, $>$ 14 kg woman, DASI score $>$ 4METs) and no other contraindication to transplantation were promoted to the transplant list, as indicated in Fig 1 [23–25].

These patients were given maintenance exercise programs to perform at the hospital's supervised transplant gym or in their home setting. Actively listed patients who lived close to the transplant center were invited to participate 1 to 5 times per week in preoperative exercise classes that focused on maintaining strength through resistance exercise and aerobic conditioning on bicycles or treadmills. Education was also provided regarding general activity for the waiting period. When travel to the hospital for exercise was not possible, a home exercise program was prescribed. Online video teleconferencing was available to patients 2 to 3 times per week to provide supervision and encouragement for exercise adherence during the waiting period.

In some cases, patients were found to be too frail to be listed immediately. When the decision to defer listing was made based on frailty concerns, physiotherapy recommendations became very focused, with clear expectations communicated to patients and families regarding activity and exercise. When possible, patients were invited to

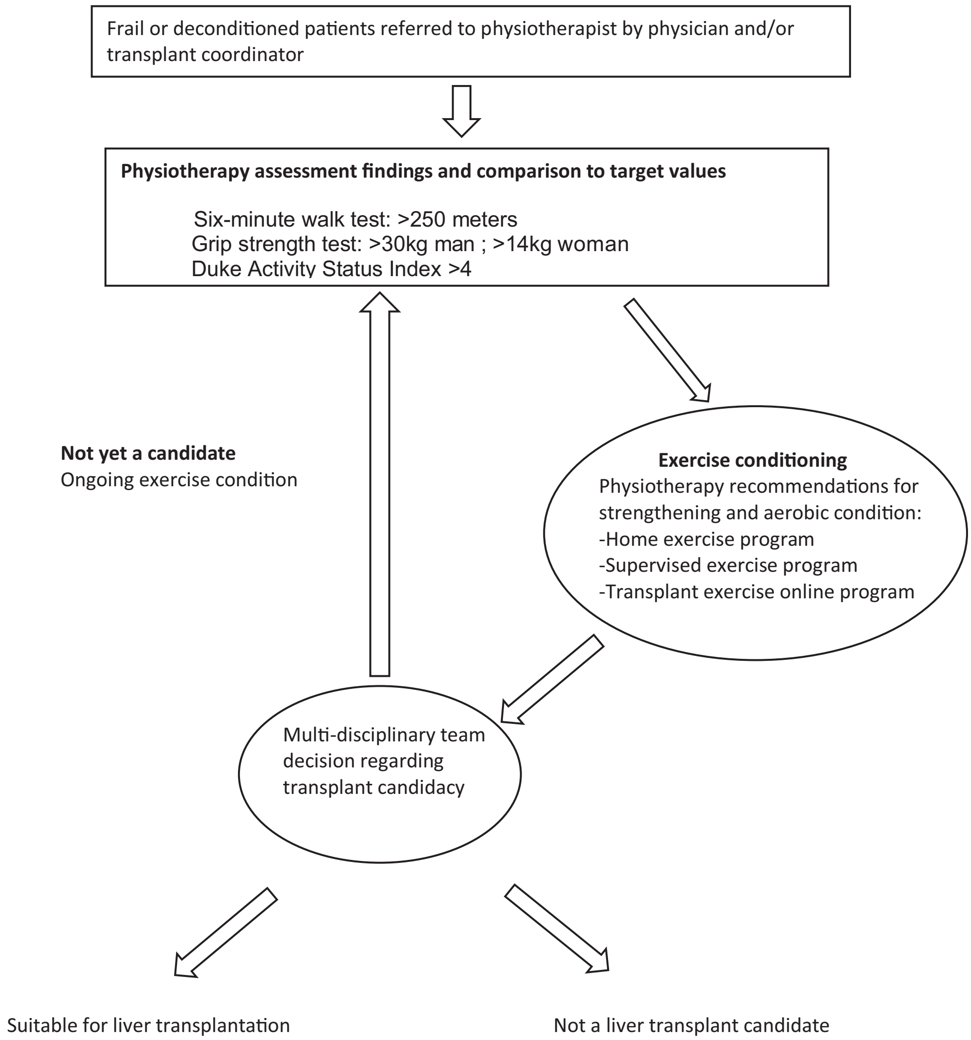

Fig 1. Model of physiotherapy care for liver transplant candidates at a Canadian transplant center.

exercise on site in the transplant gym 1 to 5 days per week. When patients lived too far to travel to the hospital for exercise, online video teleconferencing was possible in order to facilitate weekly supervised exercise and advice for progression. In all cases, education and instruction were provided regarding activity and exercise with goal setting regarding expectations for 6MWT and general activity level. When patients returned to the transplant assessment clinic for follow-up with their physician, they were re-evaluated by physiotherapy to determine if mobility targets had been reached and if they were making appropriate gains. Once the mobility targets were reached, patient cases could be reconsidered for transplant candidacy.

The goal for the physiotherapy program was to provide education regarding the benefits of activity and exercise and to provide clear examples of exercise programs for patients to follow. Whenever possible, the hospital's transplant gym was utilized to facilitate regular, supervised exercise programs, whether it be onsite or through online video-conferencing. This extended to both the patients on the waiting list as well as those who had been assessed but were not ready to be promoted to the list.

With respect to nutrition, during the pre-liver transplantation phase, both in and outpatient adults at our center who were followed by a registered dietitian were given nitrogen and energy targets based on the European Society for Enteral and Parenteral Nutrition (ESPEN) guidelines for liver disease.

OUTCOMES

The primary outcome was 90-day hospital readmission post-LT. Secondary outcomes included: length of hospital stay post-LT, postoperative complications, and mortality. Postoperative complications were surgical complications (wound infection, abdominal bleeding, biliary complications), vascular complications (portal vein thrombosis and hepatic artery thrombosis), and medical complications (infectious, nutritional, and acute rejection).

STATISTICAL ANALYSIS

Baseline variables before and after implementation of ETP were compared using the Student *t* test, Wilcoxon rank-sum test, χ^2 test, or Fisher's exact test, as appropriate. Crude analyses comparing the primary outcome, 90-day readmission, and secondary outcomes, readmission for musculoskeletal rehab, and length of hospitalization before and after the physiotherapy intervention were then performed. To control for potential confounding by changes in patient, donor, or surgical variables between the 2 time periods, multivariable regression was performed. For the primary outcome, readmission at 90 days, control for confounders was achieved through the use of propensity scores. This was necessary due to the low readmission rate in the study, the need to control for a large number of variables, and the need to avoid overfitting. A multivariable model to predict the exposure of interest, enhanced physiotherapy, was developed using predefined variables: age, sex, albumin, MELD-Na score, history of coronary artery disease, history of diabetes, length of intensive care unit stay, donor age, cold ischemic time, postop surgical complications, postop vascular complications, postop medical complications, and a propensity score assigned to each patient. Patients with similar propensity scores have a similar distribution of confounders, and the score was then used to control for all measured confounders in a logistic regression model including only the outcome of interest, exposure of interest, and the propensity score itself. Given the limited number of events for the secondary outcome, readmission for MSK rehab, a multivariable model was not developed. Lastly, the secondary outcome, length of hospitalization, was analyzed with negative binomial regression controlling for the propensity score. A two-sided *P* value $<$ .05 was considered significant. All statistical analyses were performed with Stata 14.0 (StataCorp, College Station, Tex, United States).

RESULTS

A total of 458 liver transplant patients were included in this study, 200 patients in the non-ETP group compared to 258 patients in the ETP group. Baseline patient characteristics are summarized in Table 1. The most common indication for liver transplant in the non-ETP group was viral hepatitis, mainly the hepatitis C virus, compared to hepatocellular carcinoma (HCC) in the ETP group. HCC was the indication for liver transplant in 33.6% in the ETP group versus 3.6% in the non-ETP group, *P* value $<$ .001. The median biological MELD-Na was higher in the ETP group but did not reach statistical significance (21 vs 18, *P* = .06). The ETP group were more likely to have diabetes mellitus (35.9% vs 21.5%, *P* = .001) and coronary artery disease (10.8% vs 1%, *P* $<$ .001), but other baseline characteristics were not significantly different between the two groups.

Table 1. Baseline Characteristics

	Non-ETP Group* (n = 200)	ETP Group† (n = 258)	*P* Value
Age, mean (SD)	53.4 (9.6)	56.5 (10.7)	.0015
Female, no. (%)	48 (24.1)	80 (31.9)	.070
Main cause of liver disease, no. (%)			< .001
Immune	37 (18.9)	54 (21.9)	
Viral	84 (42.6)	33 (13.4)	
Fatty liver	38 (19.3)	56 (22.7)	
Fulminate liver failure	6 (3.1)	8 (3.2)	
PCLD	5 (2.5)	2 (0.8)	
Budd-Chiari	3 (1.5)	1 (0.4)	
Metabolic	6 (3.0)	7 (2.8)	
Re-transplant	8 (4.1)	0 (0)	
Tumor	7 (3.6)	83 (33.6)	
Other	3 (1.5)	3 (1.2)	
Sodium, mean (SD)	136.2 (5.5)	134.7 (5.3)	.0038
Albumin, mean (SD)	31.0 (6.6)	33.6 (7.3)	.0001
INR, median (range)	1.4 (0.9-1.1)	1.5 (0.9-1.1)	.8697
Bilirubin, mean (SD)	115.9 (159.4)	114.4 (143.9)	.9224
Creatinine, median (range)	78.5 (31, 463)	71 (28, 1044)	.0218
MELD-NA, median (range)	18 (6, 40)	21 (4, 40)	.0600
Co-morbidities, no. (%)			
CAD	2 (1.0)	27 (10.8)	< .001
DM	43 (21.5)	90 (35.9)	.001
CKD	26 (13.0)	40 (16.4)	.317
Liver complications, no. (%)			
Hepatopulmonary syndrome	2 (1.0)	6 (2.4)	.308
Spontaneous bacterial peritonitis	3 (1.5)	15 (6.0)	.016
Length of intensive care unit stay, median	3.0	2	.0001
Donor variables			
Donor age, mean (SD)	44.7 (18.2)	48.2 (18.5)	.0436
Type of graft, no. (%)			
NDD	165 (82.5)	207 (83.5)	.460
DCD	27 (13.5)	36 (14.5)	
Living donor	8 (4.0)	5 (2.0)	
CIT, mean (SD)	401.5 (162.8)	369.4 (134.1)	.0257

Abbreviations: CAD, coronary artery disease; CIT, cold ischemic time; CKD, chronic kidney disease; DCD, donation after circulatory death; DM, diabetes mellites; MELD, the model for end stage liver disease; NDD, neurological determination of death; PCLD, polycystic liver disease.
*Nonexercise training program.
†Exercise training program.

Donors' graft variables were similar in both groups except for the mean cold ischemic time, which was lower in the ETP group compared to the non-ETP group (134.1 vs 162.8 minutes, *P* value = .025). In addition, the median length of intensive care unit stay for liver transplant candidates prior to surgery was significantly higher in the non-ETP group compared to the ETP group (3 vs 2 days, *P* value= .0001).

On crude analysis, there was no significant difference in 90-day hospital readmission (20% vs 17.9%, *P* = .576),

Table 2. Study Outcomes Stratified by Exercise Training Status

	Crude Analysis			Multivariable Analysis	
	Non-ETP Ggroup* (n = 200)	ETP Group† (n = 258)	*P* Value	Adjusted OR‡ (95% CI)	*P* Value
Readmission within 90 d, no. (%)	41 (20.0%)	45 (17.9%)	.576	0.84	.530
Readmission for Musculoskeletal rehab	1 (0.5%)	4 (1.6%)	.270	–	–
Length of hospital stay, median (range)‖	17 (5.161)	14 (3, 150)	.690	1.01¶	.885

Abbreviations: ETP, exercise training program; OR, odds ratio.
*Nonexercise training program.
†Exercise training program.
‡Adjustment based on propensity score and logistic regression.
‖Adjustment based on propensity score and negative binomial regression.
¶Represents an incidence rate ratio rather than OR.

admission for MSK rehabilitation (1 vs 4, $P = .270$), or median LOS (17 vs 14 days, $P = .690$) between non-ETP and ETP, listed in Table 2. On multivariable analysis adjusting by propensity score, there was no significant difference between 90-day readmission (OR 0.84, $P = .53$) or LOS (1.01, $P = .885$). A multivariable model was not built for MSK rehab due to the low event rate.

The postoperative surgical and vascular complications were not statically different between the 2 groups, listed in Table 3. On the other hand, the nonsurgical infection (pneumonia, urinary tract infection, clostridium difficile) rate post-liver transplant was significantly higher in the ETP group compared to the non-ETP group (17.9% vs 7%, $P = .001$).

DISCUSSION

This study aimed to evaluate the implementation of an exercise training program on reducing length of hospital stay and 90-day readmission rate post-liver transplant. There are limited publications in the literature on this patient population, and the ever-evolving field of general and transplant hepatology warrants that this question be addressed in the current era. Readmission data and length of hospital stay post-LT can be used as a barometer for the quality of health care delivered and the resource utilization required at various liver transplant centers [26,27]. In this study, the 90-day readmission rate and length of hospital stay trended toward lower levels in the ETP group compared to the non-ETP group; however, this was not statistically significant.

The 2 groups studied were from different eras in LT, the first being prior to 2012 and the second being from 2012 onward. There are a number of factors that could impact on outcomes as a result of these differences. These might include, for instance, the revolutionary therapies for hepatitis C that were introduced after 2012, as well as the increased rate of LT in patients with hepatocellular carcinoma (HCC). HCC was the main indication for liver transplant in the ETP group. This increase could be partly due to better surveillance programs for HCC, the progression of chronic liver disease in patients with viral hepatitis, and the rapidly increasing prevalence of nonalcoholic fatty liver disease [28,29]. The introduction of HCC exception points also allowed these patients to become more competitive on liver transplant waiting lists, which was implemented in Ontario in 2013 [30,31]. These factors in part may have led to the upsurge in patients with HCC being transplanted at our institute. Despite this significant increase of HCC liver transplanted patients in the ETP group, the median biological MELD-Na score was not statistically significant between the 2 groups. In fact, the ETP group had more comorbidities (coronary artery disease, diabetes, and chronic kidney diseases) compared to the non-ETP group. The presence of these comorbid conditions is associated with poor outcomes post-liver transplant [11,32].

Postoperative infections were significantly higher in the ETP group compared to the non-ETP group. Several studies have shown that the incidence of postoperative bacterial infection is high in the first month post-liver transplant, and it is associated with major cause of morbidity and mortality after liver transplant [33,34]. The presence of high comorbid conditions in the ETP group compared to the non-ETP group may have led to high postoperative bacterial infection rates in the ETP group. Postoperative surgical and vascular complications (portal vein thrombosis and hepatic artery thrombosis) were similar in both groups.

Table 3. Postoperative Complications

	Non-ETP Group* (n = 200)	ETP Group† (n = 258)	*P* Value
Post-op surgical cx, no. (%)	55 (27.5)	72 (27.9)	.923
Wound infection	11 (5.5)	14 (5.6)	.963
Abdominal bleeding	17 (8.5)	30 (12.0)	.228
Biliary complications	9 (4.5)	15 (5.9)	.317
Post-op vascular cx, no. (%)	12 (6.0)	10 (3.9)	.292
PVT‡	8 (4.0)	7 (2.8)	.476
HAT§	4 (2.0)	3 (1.2)	.492
Post-op medical cx, no. (%)	35 (17.5)	63 (24.4)	.073
Infection	14 (7.0)	45 (17.9)	.001
Nutritional	21 (10.5)	27 (10.8)	.907
Acute rejection	2 (1.0)	3 (1.2)	.844
Complete 90-day f/u, no. (%)	200 (100)	245 (95.0)	.001

Abbreviations: ETP, exercise training program; HAT, hepatic artery thrombosis; PTV, portal vein thrombosis.
*Nonexercise training program.
†Exercise training program.
‡Portal vein thrombosis.
§Hepatic artery thrombosis.

Physical frailty and sarcopenia are major sequelae of cirrhosis that contribute to an increase in morbidity and mortality in liver transplant candidates [35–38]. Beginning in 2012, our institute implemented a specialized and comprehensive physiotherapy program to better evaluate and treat frail patients, as listed in Fig 1. The 6-minute walk test (6MWT) is a proxy for aerobic conditioning, the hand-grip strength test is a measure of muscle strength and nutritional status, and the Duke Activity Status Index helps to quantify activity throughout the day. Using these tests, the physiotherapists were able to provide the liver transplant team with more objective information on baseline measure and changes to the patients' physical status prior to transplantation.

The 6MWT is a simple clinical tool that can be serially tested to document changes in a patient's physical fitness and aerobic capacity [24]. Several studies have shown that the 6MWT can predict mortality in liver transplant candidates [24]. Hand-grip strength correlates with muscle mass and has been shown to be a sensitive surrogate of body muscle mass depletion, which is a good indicator of protein energy malnutrition [39,40]. The Duke Activity Status Index (DASI) quantifies a patient's description of daily activities and converts the information into an approximate daily metabolic equivalent (MET) [23,25]. Anesthetists have used the DASI score to indicate appropriateness for major surgery, with a MET $>$ 4 being an acceptable target.

By utilizing these tools to identify fitness or malnutritional concerns, the liver transplant team was better able to define criteria for acceptance to the list [25]. In many cases, intensive physiotherapy and nutritional replacement were employed to help patients progress toward the defined targets for each of these measures. In some cases, patients were declined liver transplantation due to frailty if they failed to meet the accepted standard cutoffs (6-minute walk test $>$ 250 meters, grip strength $>$ 30 kg man $>$ 14 kg woman). This change in practice may have contributed to the trend in reduction of length of hospital stay and readmission rate in the ETP group compared to the non-ETP group; however, this was not statistically significant.

Several small studies have evaluated exercise intervention, and some included dietary counseling in patients with cirrhosis [41–44]. These studies demonstrated improvements in muscle mass, muscle strength, exercise capacity, and portal hypertension [41,43–46]. However, data of rehabilitation among liver transplant candidates with high MELD-Na or Child-Turcotte-Pugh class B/C are limited. Williams et al implemented a 10-week pilot rehabilitation program in liver transplant candidates [22].

With respect to nutrition, during the pre-liver transplantation phase, both in and outpatient adults at our center who were followed by a registered dietitian were given nitrogen and energy targets based on the European Society for Enteral and Parenteral Nutrition guidelines for liver disease [47]. A daily protein target of approximately 1.5 grams/kg (based on the estimated dry weight) was used. Supplementation was provided using a combination of oral diets; oral nutrition supplements; enteral nutrition formulas; and, in rare cases, through parenteral nutrition support. Oral nutrition supplements and tube feeding formulas were comprised of dairy proteins and the essential amino acids, which are known to stimulate muscle protein synthesis. During the acute post-transplant phase, protein targets were set higher at approximately 1.5 to 2.0 grams/kg of estimated dry weight to account for increased protein catabolism [48].

All efforts were made to avoid caloric deficits during the pre- and post-transplant phase in order to prevent accelerated loss of lean body mass. An energy target of approximately 35 kcal/kg (based on estimated dry weight) was supplied. Energy targets did not vary greatly between the pre- and post-transplant phase and were based on ESPEN guidelines [47]. Patients were also screened for micronutrient deficiencies wherever possible and supplemented, as needed, with specific vitamins and minerals.

In addition, patients were provided with an activity tracking device. Overall, the program resulted in an improvement in their 6-minute walk distance by 63 meters compared to baseline and a reduction in their frailty score on follow-up.

This study has several limitations, which include its single-center design and the generalization of its findings. As a retrospective cohort study, our results are subject to confounding and bias due to ascertainment bias. We addressed the former by measuring a large number of potential confounders and controlling them by using a propensity score and multivariable regression. There might have been residual confounding that remains unaccounted for and that could have influenced the results. Despite the study limitations, we believe our results showed that a comprehensive rehabilitation program is feasible among liver transplant candidates with high MELD-Na scores, and more studies are required to focus on establishing rehabilitation programs that target components of frailty and sarcopenia and thereby improve outcomes. Ideally, a prospective study in the current era would limit any confounding between eras and should be performed. Also, a comparison of patients with no markers of frailty pre-LT to those patients who are rehabilitated with an exercise program and then transplanted would offer further insight.

CONCLUSIONS

In conclusion, patients undergoing liver transplantation utilize significant hospital resources and have high rates of readmission. An intensive and comprehensive physiotherapy program was used to assess and treat frailty and may have contributed to a trend in decreased length of hospital stay and reduction in readmission rates in patients undergoing liver transplantation. While not statistically significant, the observed trend toward earlier discharge following liver transplantation was seen in patients enrolled in our exercise training program, even despite them being an older population, with significantly more comorbidities and postoperative infections. These results are therefore clinically significant and warrant further prospective research.

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