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# Impact of physical activity on physical function and quality of life after liver transplantation

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# ABSTRACT

**Introduction and aim of the study:** Liver-related diseases are very common in our society, and as a result, the number of people requiring liver transplantation is likewise increasing. In our research, we intended to analyze the topic of increasing survival rates and improving comfort along with the quality of life while waiting for a transplant, as well as in the postoperative period. We determined that we would investigate the impact of physical activity on risk factors that increase hospitalizations after surgery and decrease quality of life. We summarized the effect and type of exercise on sarcopenia, frailty, and their direct relation to the pre- and post-operative period of liver transplantation. In addition, we analyzed possible obstacles and difficulties arising from the implementation of physical activity in liver transplant recipients.

**Materials and methods:** The authors conducted an extensive review of articles available in PubMed, Google Scholar, UpToDate, Science Direct, and Cochrane databases. The keywords liver transplantation, physical activity, quality of life, sarcopenia, and frailty were the basis of the review. Studies published between 2001 and 2024 were included in the review.

**Results:** The vast majority of the studies emphasized the positive effects of exercise, particularly aerobic and resistance training, on improving the clinical conditions and well-being of liver transplant patients. The papers with inconsistent results nevertheless underscored the need to delve further into this topic. Thus, the overall evidence supports the inclusion of physical exercise in post-transplant care as a key strategy for improving health and quality of life.

**Conclusion**: Regular physical activity is beneficial for clinical outcomes and patients' quality of life after liver transplantation.

**Keywords:** Liver transplantation, physical activity, physical performance, quality of life, sarcopenia, frailty.

## **INTRODUCTION**

Liver transplantation (LT) is essential to prolong life and improve the quality of life for patients with liver dysfunction. There is a wide spectrum of liver failure causes that include acute liver failure and end-stage liver disease (ESLD), cirrhosis, liver cancer and acquired or genetic metabolic liver disease, viral infections, such as Hepatitis C (HCV) and Hepatitis B (HBV) (1-3). However, the most common liver-damaging factor that leads to liver failure is alcohol. Surprisingly, it is women who are more vulnerable to the adverse effects of alcohol than men, even in a small dose. Nevertheless, men represent the majority of this group (4).

In recent times, unfortunately, metabolic dysfunction-associated fatty liver disease (MAFLD) is becoming more common. The reason for this is the increasing prevalence of obesity in the population (5-7).

Another factor that has a major impact on the deterioration of liver function is a sedentary lifestyle. Inadequate lifestyle and physical inactivity increase the likelihood of conditions such as non-alcoholic fatty liver disease (NAFLD), which, when associated with obesity, leads to MAFLD, liver fibrosis, and progression of the disease to cirrhosis. A sedentary lifestyle is also closely associated with oncological risk (8). Furthermore, it is important to emphasize the fact that physical inactivity not only impairs physical function, as well as mental function, and thus also reduces the quality of life (9). What is more, a link has been observed between a sedentary lifestyle and more deaths among those on the liver transplant waiting list (10).

In the United States, the number of liver transplants has been steadily increasing over the years, culminating in a historic peak in 2022 with 9,527 transplants performed. This represents a significant 52% increase over the past decade (2012-2022), with 94.5% of the recipients constituting the adult demographic and the remaining 5.5% representing the pediatric population. Because the bottleneck in performing transplants is the limited availability of organs for transplantation relative to the number of patients in need, a waiting list has been established. Although the list has trended downward recently, there were still as many as 10,548 adult patients in the United States who are waiting for liver transplant surgery at the end of 2022. Therefore it is crucial to identify suitable recipients and make adequate qualifications for liver transplant surgery (11). In comparison, 1743 liver transplants, both single and in combination with transplantation of other organs, were performed in Europe in 2023, with 1442 people on the waiting list of recipients (12).

Due to the high demand for liver transplants in our society, which we are currently unable to meet, we are exploring ways to better prepare patients for the surgery and enhance their quality of life and post-surgery prognosis. Exercises are generally accessible and inexpensive to implement. We acquire fundamental workout knowledge from an early age in school, providing us with a wealth of exercise techniques.

Therefore, our study intended to focus on the effect of physical activity on physical function and quality of life in liver transplant patients.

## MATERIALS AND METHODS

The authors conducted an extensive review of articles available in PubMed, Google Scholar, UpToDate, Science Direct, and Cochrane databases. The keywords liver transplantation, physical activity, quality of life, sarcopenia, and frailty were the basis of the review. Studies published between 2001 and 2024 were included.

## SARCOPENIA

Researchers have identified an alternative approach to assess patients before transplantation by examining their muscular condition. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as the combination of reduced muscle mass and diminished muscle function (13). However, the latest 2018 EWGSOP2 recommendations outline decreased muscle strength as the primary parameter of sarcopenia.

The other elements, i.e., muscle quantity and physical performance, which were previously part of the main definition, are now used to determine the severity of sarcopenia (14). Various tools for diagnosing sarcopenia have been provided, such as Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) and dual-energy x-ray absorptiometry (DEXA) (15-18). Nevertheless, the various ways to measure sarcopenia are beyond the scope of this review. Sarcopenia and liver cirrhosis are closely intertwined. Figure 1 illustrates the complexity of this relationship. The predominant factors contributing to sarcopenia, as described in the 2021 practice guidelines of the American Association for the Study of Liver Disease (AASLD), encompassed malnutrition, cirrhosis-related influences, physical inactivity, other systemic factors, and environmental/organizational determinants. Nonetheless, an inactive lifestyle is considered the most crucial factor (19, 20).



#### Figure 1

Summary of pathways linking sarcopenia and myosteatosis to cirrhosis: A bi-directional communication. (21)

Numerous studies have shown that sarcopenia is a significant factor affecting both patient and graft survival after LT. Transplant recipients showed lower survival rates and extended stays in the intensive care unit (22-24). Moreover, patients diagnosed with sarcopenia after the surgery were characterized by impaired quality of life (25). It is important to address the concept of sarcopenic obesity, which denotes a condition characterized by the replacement of muscle mass with fat mass (19, 26). This medical condition represents a significant challenge due to its combination of risk factors for obesity and reduced lean mass. Furthermore, it causes reduced survival and quality of life in patients after LT (27, 28). Fortunately, there are ways to address sarcopenia and manage it properly. The most fundamental and effective strategy is engaging in physical activity. By leading an active lifestyle and exercising, individuals can increase their muscle strength (26, 29, 30).

A meta-analysis conducted by Andrea Gonzalez et al., which covered 7 studies, revealed that regular practice of resistance exercise can enhance strength and muscle mass in patients with sarcopenia and NAFLD. Consequently, they recommend this type of training as a sarcopenia treatment (31).

## FRAILTY

In the context of pre- and post-liver transplantation patient evaluation, frailty serves as an additional method for predictive assessment (32). Frailty represents a condition in which patients, as a result of their health status, experience increased susceptibility to adverse health outcomes when exposed to stressors (33). The dynamic nature of mental and physical conditions is characterized by fluctuations over time. This dynamic status applies to both areas and is subject to change. In the study, Mitnitski et al. noted that the rate of deficit accumulation is about 3% per year (34). It is estimated that between 18% and 43% of patients with cirrhosis, which we have previously mentioned as one of the leading causes of liver transplantation, are expected to be classified as frail (35, 36).

To assess frailty, physicians use a variety of scales, such as the Clinical Frailty Scale (CFS) and the Karnofsky Performance Scale (KPS), which are used in the geriatric population (37). However, these various methods of defining frailty have not yet been thoroughly studied in relation to LT. Therefore, researchers have established an already widely used method for determining frailty before liver transplantation, employing the three-component Liver Frailty Index (LFI). In fact, it can be performed at the bedside and does not consume much effort. This assessment can be easily performed at the bedside and doesn't require much effort. To execute the assessment, it is necessary to measure the grip strength of the dominant hand, time five chair squats, and observe the duration of balance in three distinct positions. Higher LFI scores indicate greater frailty intensity (38-40). The LFI provides an objective categorization of patients as robust, preliminary, or weak, a departure from the more subjective approach of the Karnofsky scale (32). Additionally, in the study done by Jutras et al., the researchers recommend that LFI should be not only for LT patients but also for other organ recipients in the pre-transplant evaluation (40).

Physicians using LFI can assess the post-liver transplant prognosis. The presence of preexisting frailty in patients is associated with diminished health status approximately one year following the procedure. Moreover, it is also linked to reduced quality of life and well-being of recipients (41). However, a significant body of evidence indicates that increasing physical activity may help reduce frailty in patients who have made lifestyle changes underscoring the role of physical activity (10, 42)

## PHYSICAL PERFORMANCE

A significant portion of liver transplant recipients declare their physical activity level as inadequate or are entirely inactive. Among those who do engage in physical activity, only a small minority practice high-quality activities (43). Physical function assessment is crucial in post-LT patients, as after such extensive surgery, due to catabolism aggravation and glucocorticosteroid therapy, at two years post-transplant muscle mass in many cases does not recover and decline in muscle strength and function can be observed as measured by knee extensor muscle strength impairment (25).

Moreover, not only is the muscle mass reduced, but also cardiorespiratory fitness is compromised, which is reflected by  $VO_2$  max reduction. All the aforementioned physical performance deficiencies may limit engagement in daily activities and heavily affect patients' lives (44).

Multiple studies analyze the impact of physical activity on physical performance in patients with end-stage liver disease and after liver transplantation (LT). Tests used in the studies to assess physical performance and associated physical frailty include a 6-minute walk test, gait speed test, timed up and go test, maximal oxygen consumption (VO<sub>2</sub> max), muscle strength including quadriceps, hamstrings, shoulder, lumbar extensor, handgrip, hip, flexion and extension of hip, elbow, shoulder, shoulder abduction, leg press, and chest press (21). What is important is the fact that these above-mentioned parameters are not detached from the patient's perspective. When asked, LT recipients identify 'functional physical fitness' as the most important primary outcome of the exercise training study (25).

In a large ambispective study involving 517 patients with end-stage liver disease, more than half listed for LT, prehabilitation, including individualized exercise prescription, resulted in a significant improvement in LFI. Nevertheless, the improvement was most substantial in fulladherent patients. Full-adherent patients reached notable progress in the 6MWT performance by the second and third follow-up visits, while all patients in general reached progress by the fourth visit. On the other hand, no significant improvement has been associated with prehabilitation in the gait speed test, however, null adherence resulted in a worsening of the gate speed test results by the third follow-up visit (45). These results are consistent with other studies on this topic. In a meta-analysis including nine studies with supervised aerobics, of which six recruited patients with compensated cirrhosis and three involved liver transplant recipients, the 6MWT results and VO2 max significantly improved after supervised exercise. These findings suggest that functional and endurance capacity, as well as cardiorespiratory fitness, are enhanced following the exercise regimen (44). Furthermore, to support findings from the above-mentioned meta-analysis, another large meta-analysis of 21 studies with solid organ transplant recipients, revealed not only the improvement in VO<sub>2</sub> max and 6MWT results in the exercise group but also quadriceps and hamstrings muscle strength capacity, leg press and chest press maximal strength (46).

Another meta-analysis, including eight full-text articles and two conference abstracts originating from eight independent studies, showed a trend for a positive impact of exercise training on cardiorespiratory fitness as measured by the 6MWT and VO<sub>2</sub> max in LT patients. Moreover, one of the studies assessed lower back and hamstring flexibility, as well as postural stability and overall motor fitness by the Timed Up and Go test and revealed significant improvement in the exercise group. Other physical performance tests used in the studies included knee extensor muscle strength and a 30-s sit-to-stand test. Three studies in the meta-analysis showed significant improvement in the 30-s sit-to-stand test and two studies showed improvement in the knee extensor muscle strength in the exercise group. Two studies revealed no difference between the control group and the exercise group in knee extensor muscle strength (25). Furthermore, some studies highlight the fact that exercise needs to be performed regularly to maintain its beneficial effects (31, 47).

#### **CLINICAL OUTCOMES**

The studies mentioned indicate that exercise improves muscle mass, and helps to tackle sarcopenia, improving LFI and physical performance assessed by various physical assessment instruments. However, these are not just isolated parameters but are closely linked to better clinical outcomes. A variety of methods are used to evaluate patients prior to receiving a liver transplant (48). One of them is The Model for End-Stage Liver Disease (MELD) scale, which includes only 3 objective variables, including total bilirubin, creatinine, and INR. The more points a patient scores on this scale, the more advanced their liver disease is. This is a valuable predictor for outcomes in patients waiting to undergo liver transplants. However, this scale is of limited value in predicting a patient's condition after surgery (49, 50).

Sarcopenia has been identified as a risk factor for pre- and post-LT mortality, longer hospitalization, waiting list dropout, and incidence of complications such as infections following LT and has been linked to higher overall healthcare costs (28, 51). Reduction in muscle mass, the core of sarcopenia, measured by the mid-arm muscle circumference is considered as a promising independent prognostic factor for mortality and post-LT outcomes in patients with decompensated cirrhosis (52). Such muscle mass reduction may also be assessed by psoas muscle mass index (PMI), which was proved at the third-month post-LT to be a predictor for 5-year survival, with higher PMI values associated with a better chance of survival (53). Moreover, when combining MELD and transversal psoas muscle thickness (MELD-psoas score), the mortality discrimination and waiting list dropout are superior to the MELD score, with sarcopenia's strong correlation to mortality after LT, negatively affecting survival after deceased-donor as well as living donor LT (23, 51).

The third lumbar skeletal muscle index (L3-SMI) and upper thigh skeletal muscle index (UT-SMI) have been validated to be other parameters used to assess sarcopenia and have been linked not only to patient survival but also to graft survival. Importantly, overall graft survival was significantly lower in the L3-SMI and UT-SMI sarcopenia groups (22). A meta-analysis of 19 studies involving 3,803 LT candidates assessing sarcopenia with CT scans, revealed an 84% higher risk of mortality on the waitlist and a 72% higher risk of post-LT mortality (37). Moreover, complications associated with liver cirrhosis, such as hepatic encephalopathy, ascites, and hepatorenal syndrome, were more frequent in patients affected with sarcopenia (19, 23).

Addressing obesity in the LT population is another important issue that needs attention. Following LT many patients experience significant weight gain, leading to overweight or obesity, with up to 85% of LT recipients gaining more than 10% of their body weight, with an average increase of 9.5 to 11.6 kg within three years, surpassing their pre-morbid weight levels (54). However, this weight gain is primarily fat rather than muscle or lean body mass (55). Obesity itself is a risk factor for longer hospital stays, venous thrombosis, and wound dehiscence after LT (56). When accompanied by sarcopenia, sarcopenic obesity poses a vital issue in LT patients creating a junction of two major comorbidities resulting in a higher risk of poor clinical outcomes than sarcopenia and obesity as separate comorbidities. Both resistance and aerobic endurance training demonstrated notable benefits in LT patients. Resistance training was proven to carry the potential to increase skeletal muscle mass, endurance training may enhance muscle function (51).

However, not only these particular types of training showed promising effects on LT patients. A study including 116 patients with liver cirrhosis on the LT waiting list revealed that every additional 500 steps taken per day results in the reduction of hospitalization risk by 5% and risk of death by 12% (57).

Concepts of sarcopenia, liver frailty, and physical performance are closely interrelated, one affecting the other. Frailty in LT patients is primarily presented as physical frailty, also linked to muscle mass reduction and decline in muscle function. As a result, frailty in patients with ESLD is strongly related to sarcopenia (10). Frailty in LT patients, as assessed with LFI, is strongly associated with pre- and post-LT outcomes. It enhances the prediction of 3-month waitlist mortality for LT candidates compared to relying solely on MELD. Additionally, it predicts post-LT functional status and longitudinal assessment of LFI offers valuable insight into mortality risk (32). Frail patients achieve worse results in physical performance tests, including less walking distance in the 6MWT and gait speed test, less sit and stand up, and lower isometric knee extension strength and grip strength (10, 37). Furthermore, LFI values are the lowest in physically active LT patients, while the highest values, meaning higher frailty intensity, are exhibited by individuals with a sedentary lifestyle (10).

As mentioned, frailty is associated with sarcopenia, and these two intertwine, resulting in worse physical performance and, therefore, worse clinical outcomes. In ESLD patients, physical frailty was proven to be associated with higher mortality risk. LFI values greater than 4.5 were related to an 82% increase in the risk of waitlist mortality among LT outpatient candidates, independent of the MELD-NA score, ascites, and hepatic encephalopathy. It was estimated that around 50% of LT candidates may experience a worsening in LFI and an increase of 0.1 after 3 months is associated with a twofold increase in waitlist mortality risk, whereas improvement in the LFI between 0.2 and 0.4 provided a survival advantage, especially in frail patients (28, 45). Moreover, frailty has been associated with a higher risk of decompensation mortality post-LT, overall post-LT mortality, greater healthcare resource utilization, longer ICU and hospital stays, and a higher likelihood of non-home discharge. These can be also observed when assessing frailty with Karnofsky Performance Status (KPS). KPS values below 40% pre-LT were linked to a 38% increased risk of graft failure, 43% higher risk of mortality and longer hospital stay after LT surgery, and higher healthcare costs in the first year post-LT. Additionally, higher KPS values, meaning higher performance status and lower frailty intensity, were associated with shorter intubation time after LT surgery (37). However, it is worth mentioning that in a large ambispective cohort study, while LFI, 6MWT, and GST individually predicted survival, improvements in the 6MWT did not lead to better survival outcomes, and only LFI remained significant when all three instruments were included in the same model. The variable that was related to improved survival after adjusting for baseline frailty and other liveradjusted parameters was adherence to the prehabilitation program including exercise training (45). In a cohort of 214 LT patients, only 40% of patients were considered physically robust one year post-LT. Initially, after LT, frailty scores worsened at 3 months post-LT, returned to pretransplant baseline transplantation at 6 months, and later on showed modest improvement by 12 months. The most significant predictor of being robust post-LT was high physical activity pre-LT, once again highlighting the importance of prehabilitation (37, 42).

A recent study including 98 post-LT patients showed negative effects of sarcopenia on cardiopulmonary performance, such as decreased VO<sub>2</sub> max and elevated levels of a prognostic marker in cardiovascular diseases - NT-proBNP pre-LT (24, 58). It is vital to highlight the fact that 19% of post-LT deaths are caused by cardiovascular diseases (CVD) and most NAFLD patients will die from either a CVD event or extrahepatic cancers rather than from a major adverse liver outcome, CVD being the leading cause of death in NAFLD patients (8, 54). Therefore, it is of utmost priority to reduce cardiovascular risk in LT patients. Recent studies underscore the role of exercise training and physical activity in cardiovascular risk reduction in LT patients. Given that many LT recipients exhibit risk factors like obesity, hypertension, diabetes, and dyslipidemia, lifestyle modifications, including dietary changes and increased physical activity, are essential (54, 59). The high prevalence of metabolic syndrome and cardiovascular complications among LT recipients further emphasizes the need for increased physical activity and improved physical function as primary modifiable risk factors (37, 42). Furthermore, reduced exercise capacity in solid organ transplant recipients was linked to diabetes, cardiovascular complications, and higher mortality, while impairing their quality of life.

Exercise training has been shown to improve maximal exercise capacity and diastolic blood pressure in solid organ transplant recipients. Although there is limited evidence that exercise training affects other cardiovascular risk factors, improvements in VO2 peak, a key predictor of cardiovascular disease risk and mortality, have been observed. In the meta-analysis involving solid organ transplant recipients, it was proven that exercise training enhances VO2 max and reduces diastolic blood pressure compared to controls, irrespective of the duration, frequency, or timing of exercise, thus reducing cardiovascular risk (46). Exercise training has also been shown to improve other cardiovascular biomarkers, reverse endothelial dysfunction, and enhance body composition by reducing adipose tissue and possibly increasing lean body mass. All the above-mentioned arguments for cardiovascular risk reduction resonate in the Roundtable Statement from the American College of Sports Medicine that highlights the role of regular physical activity in NAFLD prevention and recommends that all NAFLD patients should be screened for physical activity and counseled on the benefits of it (8).

## **QUALITY OF LIFE**

Quality of Life (QoL) in LT recipients includes physical, psychological, and social dimensions. Its assessment typically involves Short Form 36 (SF-36), which covers physical function, emotional well-being, social functioning, and general health perceptions. Other validated instruments include health-related quality of life (HRQoL) encompassing mobility, self-care, and daily functioning and patient-reported outcomes (PROs) that provide patients' insights on their daily functioning, routine activities, and overall mental health (60, 61).

QoL in LT recipients generally improves significantly after the procedure, but it varies across different domains and is influenced by several factors. Immediately post-LT, the majority of patients experience a notable increase in their overall QoL, which is attributed to improvements in physical, psychological, and social functioning dimensions. In the covered studies, a reduction in pain and discomfort, along with improved self-care abilities, have been noted. Moreover, many patients report improvement in the mental health aspect of QoL with anxiety and depression reduction (60).

However, despite a visible increase in these aspects, LT recipients often report an overall lower QoL than the general population. Although the aspects mentioned above improve after LT, other comorbidities and persistent fatigue and sleep disturbances still negatively affect overall QoL. Conditions that often coincide in LT patients, such as diabetes, obesity, and cardiovascular disease, as well as challenges, including immunosuppressive therapy management and its side effects, were proven to be significant factors influencing both physical and mental health. As a result, LT recipients exhibit a complex profile of QoL, which requires careful and individualized management (9, 25, 62). It's important to note that the quality of life for LT recipients is influenced not only by psychological and health factors but also by social aspects such as the ability to return to work and participate in social activities. Even though many patients regain their roles in family and social settings, some of them, especially the ones with surgical complications and prolonged recovery periods, still struggle with social isolation and role limitations (42, 61).

Physical activity plays a critical role in determining the quality of life for transplant recipients. Numerous studies have demonstrated that engaging in physical activity after a liver transplant significantly enhances the quality of life in various aspects, such as physical functioning, mobility, and mental health. Interventions involving exercise, including resistance and aerobic training, as well as participation in group sports, have been shown to improve muscle strength, cardiorespiratory fitness, and overall physical function. The lack of physical activity and sedentary behavior are consistently associated with a decreased quality of life. This underscores the importance of targeted efforts to promote regular physical activity among transplant recipients. The positive association between physical activity and quality of life is observed across different types of transplant populations, underscoring the therapeutic value of exercise (42, 63, 64).

## **OBSTACLES IN EXERCISE PROGRAMS**

Conducting exercise programs for LT patients presents several challenges, ranging from safety concerns to logistical and financial barriers. Historically, the primary obstacle has been the concern over the safety of exercise, particularly in patients with portal hypertension, a common complication in those with end-stage liver disease. Exercising was believed to potentially exacerbate portal pressure, leading to serious complications such as variceal bleeding. Therefore, all exercises in LT patients were approached with skepticism and caution. However, recent studies have challenged this notion, demonstrating that with appropriate variceal prophylaxis, exercise is not only safe but also beneficial in reducing portal pressure in patients who are overweight or obese and have portal hypertension. Another consideration is the comorbidities of LT recipients. Patients with uncontrolled hypertension or severe cardiopulmonary diseases may require additional precautions or may be deemed unsuitable for exercise programs. Ensuring that these patients are properly screened and monitored is essential to minimize risks and enhance the benefits of physical activity in this population This highlights the importance of a tailored approach to exercise, considering the patient's general health and physical abilities (10, 37, 44).

The financial burden associated with structured exercise programs is another issue that needs to be faced when designing an exercise program for LT recipients.

Supervised training programs often require careful monitoring and supervision, which can be resource-intensive and costly (37). Moreover, the vast majority of supervised exercise sessions require frequent visits to rehabilitation centers, posing a logistical challenge, especially for patients living in remote areas. To address these issues, there has been a growing interest in remote monitoring and telehealth interventions. Emerging evidence suggests that these approaches can be just as safe and effective as traditional in-person exercise programs, offering a more flexible and accessible option for LT patients. Wearable technology can play a role in monitoring physical activity, ensuring that patients engage in safe levels of exercise, while providing real-time feedback to both patients and healthcare providers (8, 65).

## CONCLUSIONS

Physical activity plays a crucial role in improving physical function, quality of life, and clinical outcomes in liver transplant recipients. While liver transplant surgery is essential for treating end-stage liver disease and improving survival, recipients often face challenges such as sarcopenia, frailty, and reduced quality of life due to chronic liver disease, comorbidities, and prolonged inactivity. Regular exercise, including aerobic and resistance training, has been shown to enhance muscle strength, cardiorespiratory fitness, and physical performance, helping to counteract conditions like sarcopenia and frailty that can negatively impact clinical outcomes. Additionally, regular exercise can lead to improved physical and mental health, reduced fatigue, and enhanced social well-being for liver transplant recipients. However, it's important to note that some studies have shown limited or inconsistent effects of exercise on clinical outcomes and quality of life, indicating a need for further research to fully understand the impact of physical activity on this population. Despite these discrepancies, the overall evidence supports the integration of physical activity into post-transplant care as a key strategy for optimizing health and well-being.

#### **ABBREVIATIONS**

LT	Liver transplantation
ESLD	End-stage liver disease
HCV	Hepatitis C
HBV	Hepatitis B
MAFLD	Metabolic dysfunction-associated fatty liver disease
NAFLD	Non-alcoholic fatty liver disease
EWGSOP	European Working Group on Sarcopenia in Older People
СТ	Computed Tomography
MRI	Magnetic Resonance Imaging
DEXA	Dual-energy x-ray absorptiometry
AASLD	American Association for the Study of Liver Disease
CFS	Clinical Frailty Scale
KPS	Karnofsky Performance Scale
LFI	Liver Frailty Index
VO <sub>2</sub> max	Maximal oxygen consumption
6MWT	6-minute walk test
MELD	Model for End-Stage Liver Disease

INR	International normalized ratio	
PMI	Psoas muscle mass index	
MELD-psoas score MELD and transversal psoas muscle thickness		
L3-SMI	Third lumbar skeletal muscle index	
UT-SMI	Upper thigh skeletal muscle index	
ICU	Intensive-care unit	
GST	Gait Speed Test	
NT-proBNP	N-terminal prohormone of brain natriuretic peptide	
CVD	Cardiovascular diseases	
VO₂ peak	Peak oxygen consumption	
QoL	Quality of Life	
SF-36	Short Form 36	
HRQoL	Health-related quality of life	
PROs	Patient-reported outcomes	

# DISCLOSURE

## Author's contribution:

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# REFERENCES

1. Mahmud N. Selection for Liver Transplantation: Indications and Evaluation. Curr Hepatol Rep. 2020;19(3):203-12.

2. Fox AN, Brown RS, Jr. Is the patient a candidate for liver transplantation? Clin Liver Dis. 2012;16(2):435-48.

3. Hamoir C, Horsmans Y, Stärkel P, Dahlqvist G, Negrin Dastis S, Lanthier N. Risk of hepatocellular carcinoma and fibrosis evolution in hepatitis C patients with severe fibrosis or cirrhosis treated with direct acting antiviral agents. Acta Gastroenterol Belg. 2021;84(1):25-32.

4. Roerecke M, Vafaei A, Hasan OSM, Chrystoja BR, Cruz M, Lee R, et al. Alcohol Consumption and Risk of Liver Cirrhosis: A Systematic Review and Meta-Analysis. Am J Gastroenterol. 2019;114(10):1574-86.

5. Sangro P, de la Torre Aláez M, Sangro B, D'Avola D. Metabolic dysfunction-associated fatty liver disease (MAFLD): an update of the recent advances in pharmacological treatment. J Physiol Biochem. 2023;79(4):869-79.

6. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet. 2011;377(9765):557-67.

7. Lanthier N, Vanuytsel T. Metabolic dysfunction-associated fatty liver disease: a new clearer nomenclature with positive diagnostic criteria. Acta Gastroenterol Belg. 2020;83(4):513-5.

8. Stine JG, Long MT, Corey KE, Sallis RE, Allen AM, Armstrong MJ, et al. Physical Activity and Nonalcoholic Fatty Liver Disease: A Roundtable Statement from the American College of Sports Medicine. Med Sci Sports Exerc. 2023;55(9):1717-26.

9. Gitto S, Golfieri L, Mannelli N, Tamè MR, Lopez I, Ceccato R, et al. Quality of life in liver transplant recipients during the Corona virus disease 19 pandemic: A multicentre study. Liver Int. 2022;42(7):1618-28.

10. Loschi TM, Baccan M, Della Guardia B, Martins PN, Boteon A, Boteon YL. Exercise training as an intervention for frailty in cirrhotic patients on the liver transplant waiting list: A systematic review. World J Hepatol. 2023;15(10):1153-63.

11. OPTN/SRTR 2022 Annual Data Report: Liver [Internet]. The Scientific Registry ofTransplantRecipients2022.Availablefrom:https://srtr.transplant.hrsa.gov/annual reports/2022/Liver.aspx.

12. Eurotransplant Statistics Report Library [Internet]. 2023. Available from: https://statistics.eurotransplant.org/.

13. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23.

14. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-31.

15. Tandon P, Mourtzakis M, Low G, Zenith L, Ney M, Carbonneau M, et al. Comparing the Variability Between Measurements for Sarcopenia Using Magnetic Resonance Imaging and Computed Tomography Imaging. Am J Transplant. 2016;16(9):2766-7.

16. Praktiknjo M, Book M, Luetkens J, Pohlmann A, Meyer C, Thomas D, et al. Fat-free muscle mass in magnetic resonance imaging predicts acute-on-chronic liver failure and survival in decompensated cirrhosis. Hepatology. 2018;67(3):1014-26.

17. Lindqvist C, Brismar TB, Majeed A, Wahlin S. Assessment of muscle mass depletion in chronic liver disease: Dual-energy x-ray absorptiometry compared with computed tomography. Nutrition. 2019;61:93-8.

18. Sinclair M, Hoermann R, Peterson A, Testro A, Angus PW, Hey P, et al. Use of Dual X-ray Absorptiometry in men with advanced cirrhosis to predict sarcopenia-associated mortality risk. Liver Int. 2019;39(6):1089-97.

19. Lai JC, Tandon P, Bernal W, Tapper EB, Ekong U, Dasarathy S, et al. Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021;74(3):1611-44.

20. Abate M, Di Iorio A, Di Renzo D, Paganelli R, Saggini R, Abate G. Frailty in the elderly: the physical dimension. Eura Medicophys. 2007;43(3):407-15.

21. Goffaux A, Delorme A, Dahlqvist G, Lanthier N. Improving the prognosis before and after liver transplantation: Is muscle a game changer? World J Gastroenterol. 2022;28(40):5807-17.

22. Lim M, Kim JM, Yang J, Kwon J, Kim KD, Jeong ES, et al. Upper thigh skeletal muscle index predicts outcomes in liver transplant recipients. Ann Surg Treat Res. 2023;105(4):219-27.

23. Trovato FM, Artru F. Nutritional optimization in liver transplant patients: from the pretransplant setting to post-transplant outcome. Acta Gastroenterol Belg. 2023;86(2):335-42.

24. Miarka M, Gibiński K, Janik MK, Główczyńska R, Zając K, Pacho R, et al. Sarcopenia-The Impact on Physical Capacity of Liver Transplant Patients. Life (Basel). 2021;11(8).

25. De Smet S, O'Donoghue K, Lormans M, Monbaliu D, Pengel L. Does Exercise Training Improve Physical Fitness and Health in Adult Liver Transplant Recipients? A Systematic Review and Meta-analysis. Transplantation. 2023;107(1):e11-e26.

26. Dhillon RJ, Hasni S. Pathogenesis and Management of Sarcopenia. Clin Geriatr Med. 2017;33(1):17-26.

27. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629-35.

28. Tandon P, Montano-Loza AJ, Lai JC, Dasarathy S, Merli M. Sarcopenia and frailty in decompensated cirrhosis. J Hepatol. 2021;75 Suppl 1(Suppl 1):S147-s62.

29. Ramsey KA, Rojer AGM, D'Andrea L, Otten RHJ, Heymans MW, Trappenburg MC, et al. The association of objectively measured physical activity and sedentary behavior with skeletal muscle strength and muscle power in older adults: A systematic review and meta-analysis. Ageing Res Rev. 2021;67:101266.

30. Lu L, Mao L, Feng Y, Ainsworth BE, Liu Y, Chen N. Effects of different exercise training modes on muscle strength and physical performance in older people with sarcopenia: a systematic review and meta-analysis. BMC Geriatr. 2021;21(1):708.

31. Gonzalez A, Valero-Breton M, Huerta-Salgado C, Achiardi O, Simon F, Cabello-Verrugio C. Impact of exercise training on the sarcopenia criteria in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Eur J Transl Myol. 2021;31(1).

32. Mohan R, Kalra A. Nutrition, frailty assessment, and interventions for the liver transplant candidate. Clin Liver Dis (Hoboken). 2023;22(1):23-8.

33. Walston J, Hadley EC, Ferrucci L, Guralnik JM, Newman AB, Studenski SA, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. J Am Geriatr Soc. 2006;54(6):991-1001.

34. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal. 2001;1:323-36.

35. Cron DC, Friedman JF, Winder GS, Thelen AE, Derck JE, Fakhoury JW, et al. Depression and Frailty in Patients With End-Stage Liver Disease Referred for Transplant Evaluation. Am J Transplant. 2016;16(6):1805-11.

36. Tandon P, Tangri N, Thomas L, Zenith L, Shaikh T, Carbonneau M, et al. A Rapid Bedside Screen to Predict Unplanned Hospitalization and Death in Outpatients With Cirrhosis: A Prospective Evaluation of the Clinical Frailty Scale. Am J Gastroenterol. 2016;111(12):1759-67.

37. Tandon P, Zanetto A, Piano S, Heimbach JK, Dasarathy S. Liver transplantation in the patient with physical frailty. J Hepatol. 2023;78(6):1105-17.

38. Francisco UoS. Functional Assessment in Liver Transplantation: University of San Francisco [Liver Frailty Index]. Available from: <u>https://liverfrailtyindex.ucsf.edu/</u>.

39. 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(2):564-74.

40. Jutras G, Lai JC. The Liver Frailty Index: a model for establishing organ-specific frailty metrics across all solid organ transplantation. Curr Opin Organ Transplant. 2024;29(4):266-70.

41. Lai JC, Shui AM, Duarte-Rojo A, Rahimi RS, Ganger DR, Verna EC, et al. Association of Frailty With Health-Related Quality of Life in Liver Transplant Recipients. JAMA Surg. 2023;158(2):130-8.

42. Dunn MA, Rogal SS, Duarte-Rojo A, Lai JC. Physical Function, Physical Activity, and Quality of Life After Liver Transplantation. Liver Transpl. 2020;26(5):702-8.

43. Gitto S, Golfieri L, Gabrielli F, Falcini M, Sofi F, Tamè MR, et al. Physical activity in liver transplant recipients: a large multicenter study. Intern Emerg Med. 2024;19(2):343-52.

44. Choo YJ, Cho CW, Chang MC. Effects of supervised exercise on aerobic capacity and quality of life in patients with chronic liver disease and patients who underwent liver transplantation: a systematic review and meta-analysis. Int J Rehabil Res. 2022;45(1):1-11.

45. Lin FP, Visina JM, Bloomer PM, Dunn MA, Josbeno DA, Zhang X, et al. Prehabilitation-Driven Changes in Frailty Metrics Predict Mortality in Patients With Advanced Liver Disease. Am J Gastroenterol. 2021;116(10):2105-17.

46. Janaudis-Ferreira T, Tansey CM, Mathur S, Blydt-Hansen T, Lamoureaux J, Räkel A, et al. The effects of exercise training in adult solid organ transplant recipients: A systematic review and meta-analysis. Transpl Int. 2021;34(5):801-24.

47. Cappelle M, Masschelein E, Vos R, Van Remoortel H, Smets S, Vanbekbergen J, et al. High-Intensity Training for 6 Months Safely, but Only Temporarily, Improves Exercise Capacity in Selected Solid Organ Transplant Recipients. Transplant Proc. 2021;53(6):1836-45.

48. Minich A, Arisar FAQ, Shaikh NS, Herman L, Azhie A, Orchanian-Cheff A, et al. Predictors of patient survival following liver transplant in non-alcoholic steatohepatitis: A systematic review and meta-analysis. EClinicalMedicine. 2022;50:101534.

49. Kanwal F, Dulai GS, Spiegel BM, Yee HF, Gralnek IM. A comparison of liver transplantation outcomes in the pre- vs. post-MELD eras. Aliment Pharmacol Ther. 2005;21(2):169-77.

50. Peng Y, Qi X, Guo X. Child-Pugh Versus MELD Score for the Assessment of Prognosis in Liver Cirrhosis: A Systematic Review and Meta-Analysis of Observational Studies. Medicine (Baltimore). 2016;95(8):e2877.

51. Reichelt S, Pratschke J, Engelmann C, Neumann UP, Lurje G, Czigany Z. Body composition and the skeletal muscle compartment in liver transplantation: Turning challenges into opportunities. Am J Transplant. 2022;22(8):1943-57.

52. Kalafateli M, Mantzoukis K, Choi Yau Y, Mohammad AO, Arora S, Rodrigues S, et al. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the Model for End-stage Liver Disease score. J Cachexia Sarcopenia Muscle. 2017;8(1):113-21.

53. Tsao YT, Lee WC, Huang CH, Lin IH, Huang YY. A comprehensive investigation of nutritional status and psoas muscle mass in predicting five-year survival in patients with liver transplant. J Formos Med Assoc. 2022;121(7):1317-24.

54. Spillman LN, Madden AM, Richardson H, Imamura F, Jones D, Nash M, et al. Nutritional Intake after Liver Transplant: Systematic Review and Meta-Analysis. Nutrients. 2023;15(11).

55. Oikonomou IM, Sinakos E, Antoniadis N, Goulis I, Giouleme O, Anifanti M, et al. Effects of an active lifestyle on the physical frailty of liver transplant candidates. World J Transplant. 2022;12(11):365-77.

56. Ruck JM, Shui AM, Jefferis AA, Duarte Rojo A, Rahimi RS, Ganger DR, et al. Association of body mass index with post-liver transplant outcomes. Clin Transplant. 2024;38(1):e15205.

57. Lin FP, Bloomer PM, Grubbs RK, Rockette-Wagner B, Tevar AD, Dunn MA, et al. Low Daily Step Count Is Associated With a High Risk of Hospital Admission and Death in Community-Dwelling Patients With Cirrhosis. Clin Gastroenterol Hepatol. 2022;20(8):1813-20.e2.

58. Goetze JP, Bruneau BG, Ramos HR, Ogawa T, de Bold MK, de Bold AJ. Cardiac natriuretic peptides. Nat Rev Cardiol. 2020;17(11):698-717.

59. Onghena L, Berrevoet F, Vanlander A, Van Vlierberghe H, Verhelst X, Hoste E, et al. Illness cognitions and health-related quality of life in liver transplant patients related to length of stay, comorbidities and complications. Qual Life Res. 2022;31(8):2493-504.

60. Raju S, Mathew JS, S S, Padma UD. Quality of life 5 years following liver transplantation. Indian J Gastroenterol. 2021;40(4):353-60.

61. Kaplan A, Korenjak M, Brown RS, Jr. Post-liver transplantation patient experience. J Hepatol. 2023;78(6):1234-44.

62. Getsuwan S, Tanpowpong P, Lertudomphonwanit C, Chuthapisith J, Butsriphum N, Prabpram W, et al. Health-Related Quality of Life in Pediatric Liver Transplant Recipients. Transplant Proc. 2021;53(1):141-7.

63. Mulder MB, Busschbach JV, van Hoek B, van den Berg AP, Polak WG, Alwayn IPJ, et al. Health-related Quality of Life and Fatigue in Liver Transplant Recipients Receiving Tacrolimus Versus Sirolimus-based Immunosuppression: Results From a Randomized Trial. Transplantation. 2023;107(12):2545-53.

64. Hager A, Guo Y, Wang Y, Mazurak V, Gilmour SM, Mager DR. Exercise rehabilitation to treat sarcopenia in pediatric transplant populations. Pediatr Transplant. 2023;27(8):e14602.

65. Hickman IJ, Hannigan AK, Johnston HE, Elvin-Walsh L, Mayr HL, Staudacher HM, et al. Telehealth-delivered, Cardioprotective Diet and Exercise Program for Liver Transplant Recipients: A Randomized Feasibility Study. Transplant Direct. 2021;7(3):e667.