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# PREHABILITATION IN PATIENTS AWAITING LIVER TRANSPLANTATION – A REVIEW OF CURRENT EVIDENCE

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**ABSTRACT**

End-stage liver disease (ESLD) is associated with significant metabolic disturbances, including chronic inflammation, hypercatabolism, and impaired protein synthesis, which lead to the development of sarcopenia and frailty. These conditions are common among patients qualified for liver transplantation and represent independent risk factors for waitlist mortality, postoperative complications, and prolonged hospitalization.

Prehabilitation, defined as a multimodal intervention including physical training, nutritional optimization, and psychological support, aims to improve the patient's physiological reserve prior to surgery. The aim of this study was a systematic evaluation of the available evidence regarding prehabilitation in liver transplant candidates, with particular emphasis on its impact on physical performance and clinical outcomes.

Available data indicate that prehabilitation improves performance parameters such as VO<sub>2</sub>peak and the 6-minute walk distance. However, its impact on hard clinical endpoints, including mortality and postoperative complications, remains inconclusive.

Prehabilitation appears to be a safe and potentially beneficial intervention, particularly in frail patients; however, further high-quality studies are required.

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**KEYWORDS**

End-Stage Liver Disease, Liver Transplantation, Prehabilitation, Frailty, Sarcopenia, Physical Performance

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**Introduction**

End-stage liver disease is associated with profound metabolic disturbances, including chronic inflammation, hypercatabolism, and impaired protein synthesis, which contribute to the development and progression of sarcopenia and frailty [1]. These conditions are common among patients qualified for liver transplantation—sarcopenia is observed in 40–60% of patients, while frailty occurs in approximately 25% [2].

Liver transplantation remains the only effective treatment for end-stage liver disease; however, the procedure itself represents a substantial physiological burden for which many patients are insufficiently prepared due to reduced functional reserve. It has been shown that patients with frailty and sarcopenia are at increased risk of pre-transplant mortality, higher rates of hospital readmissions, and greater healthcare costs [3,4].

In this context, frailty and reduced physical performance are considered potentially modifiable risk factors that may influence both perioperative course and long-term outcomes. Prehabilitation, defined as a multimodal intervention including physical training, nutritional optimization, and psychological support, aims to enhance the patient's physiological reserve prior to surgery. Available evidence suggests that structured exercise programs in liver transplant candidates may lead to improvements in aerobic capacity, muscle strength, and frailty parameters, which may potentially translate into better clinical outcomes [5–12].

Despite the growing interest in this topic, the available evidence remains heterogeneous, and clear clinical recommendations are still limited. Therefore, the aim of this study is to systematically evaluate the current evidence regarding prehabilitation in liver transplant candidates.

**Aim of the study:** To evaluate the available scientific evidence on the impact of prehabilitation on physical performance, frailty severity, and selected clinical outcomes in patients awaiting liver transplantation.

**Research questions:**

- How does prehabilitation affect physical performance in patients awaiting liver transplantation?
- How does prehabilitation influence the length of hospital stay in patients after liver transplantation?
- How does prehabilitation affect frailty severity in patients after liver transplantation?

**Research hypotheses:**

- Prehabilitation improves physical performance parameters in patients awaiting liver transplantation.
- Prehabilitation may reduce the length of hospital stay after liver transplantation.
- Patients undergoing prehabilitation demonstrate improvement in frailty index scores.

**Materials and Methods**

**Population**

The study population consisted of adult patients with end-stage liver disease (ESLD) qualified for liver transplantation.

**Intervention, comparator, and outcomes**

The intervention consisted of multimodal prehabilitation including structured physical training (aerobic and/or resistance), with optional nutritional and/or psychological support.

The comparator was standard care or the absence of a structured prehabilitation program.

The outcomes included: frailty, sarcopenia, physical performance (VO<sub>2</sub>peak, 6-minute walk test), postoperative complications, length of hospital stay, and mortality.

**Inclusion and Exclusion Criteria**

**Inclusion criteria:**

- studies involving adult patients with ESLD qualified for liver transplantation,
- interventional and observational studies evaluating the impact of pre-transplant physical conditioning,
- studies reporting at least one of the predefined outcomes,
- randomized controlled trials, cohort studies, and pilot studies.

**Exclusion criteria:**

- case reports, review articles, and editorial comments,
- studies not involving liver transplant candidates,
- rehabilitation conducted exclusively after transplantation.

**Data collection, study analysis, and statistical methods**

The literature review was conducted using the PubMed database. The search included publications published up to March 2026.

The following search strategy was applied:

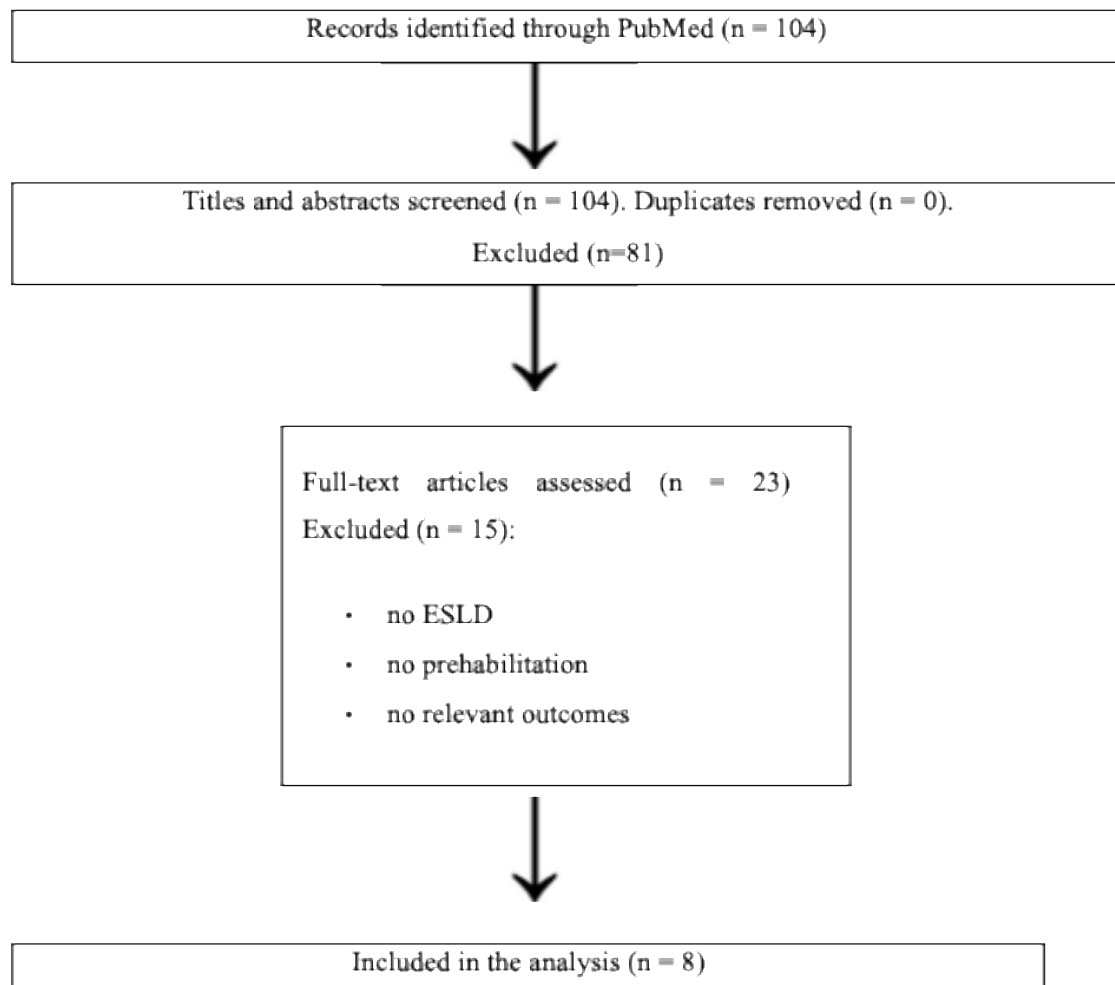
("liver transplantation" OR "liver transplant candidates" OR "end-stage liver disease" OR ESLD)

AND

(prehabilitation OR "exercise training" OR "physical training" OR rehabilitation)

AND

(frailty OR sarcopenia OR "physical capacity" OR "exercise capacity" OR outcomes OR complications)



*Fig. 1. PRISMA flow diagram of study selection.*

### Artificial Intelligence (AI)

AI tools were used exclusively for the preliminary extraction of data from abstracts, identification of recurring keywords to optimize the search process, and linguistic refinement of the final manuscript. All analyses and interpretations are the original work of the authors.

### Data Extraction

The following data were extracted from the selected studies:

- population characteristics,
- duration of the intervention,
- assessed outcomes,
- key findings.

Theoretical Background

### Pathophysiology of Frailty

Frailty is defined as a state of reduced physiological reserve and increased vulnerability to stressors. In the course of end-stage liver disease, its development is closely associated with loss of muscle mass, reduced physical activity, and nutritional disturbances. A decline in skeletal muscle mass, strength, and function is defined as sarcopenia [13].

One of the key mechanisms leading to the development of sarcopenia in liver cirrhosis is hyperammonemia. Under physiological conditions, ammonia produced in the body is metabolized in the liver through the urea cycle. In end-stage liver disease, this process is impaired, resulting in increased blood ammonia levels. Detoxification of ammonia shifts to skeletal muscle, where branched-chain amino acids (BCAAs) are utilized for glutamine synthesis. This reduces the availability of BCAAs for muscle protein synthesis, thereby impairing muscle regeneration and maintenance [14].

In addition to reduced muscle protein synthesis, increased protein degradation plays a significant role. Hyperammonemia has been shown to induce autophagy in skeletal muscle, representing an important mechanism of proteolysis in liver cirrhosis [15]. At the same time, increased expression of myostatin, mitochondrial dysfunction, and elevated production of reactive oxygen species further enhance catabolic processes and contribute to the development of hepatic myopathy [1].

Hormonal disturbances also play a significant role in the pathogenesis of sarcopenia and frailty, including reduced levels of testosterone and insulin-like growth factor 1 (IGF-1), as well as insulin resistance, all of which impair anabolic signaling pathways in muscle. Additionally, chronic inflammation associated with elevated levels of proinflammatory cytokines and alterations in the gut microbiota (dysbiosis) may contribute to muscle wasting [16].

The consequence of the described disturbances is the development of frailty, which in patients with ESLD constitutes an independent risk factor for mortality, hospitalization, and perioperative complications. In the context of liver transplantation, which represents a significant metabolic burden, the presence of sarcopenia and frailty is associated with a reduced capacity of the organism to adapt to perioperative stress, resulting in poorer clinical outcomes.

Understanding the above mechanisms indicates that interventions aimed at improving physical performance and nutritional status have a biological rationale and may influence the course of the disease. According to the recommendations of the International Liver Transplantation Society, prehabilitation is considered a component of perioperative care and is recognized as a safe and potentially beneficial intervention for improving patients' functional status [17].

#### **Clinical Significance of Frailty**

Sarcopenia can be assessed objectively, primarily based on imaging studies such as computed tomography, which is routinely performed in liver transplant candidates. The most commonly used method is the assessment of muscle cross-sectional area at the level of the third lumbar vertebra (L3), which correlates with total body muscle mass [18].

Frailty can also be assessed using validated tools such as the Liver Frailty Index (LFI), which includes handgrip strength measurement, a chair stand test, and balance assessment [19]. Unlike sarcopenia, which primarily refers to muscle mass and function, frailty represents a broader clinical construct encompassing the overall functional reserve of the organism.

Assessment of both sarcopenia and frailty is of significant clinical importance, as these are potentially modifiable factors. It has been shown that the presence of frailty in liver transplant candidates is associated with an increased risk of waitlist mortality, independent of disease severity as assessed by the MELD score [20].

Moreover, patients with frailty are more frequently hospitalized, have a higher risk of perioperative complications, and exhibit poorer post-transplant outcomes [3,4]. This indicates that functional status assessment provides prognostic information beyond traditional biochemical parameters.

Given that the waiting time for liver transplantation may range from several weeks to several months, this period represents a potential therapeutic window for interventions aimed at improving physical performance and nutritional status.

#### **Definition and Components of Prehabilitation**

Prehabilitation is a preoperative intervention aimed at enhancing physiological reserve and improving functional capacity in patients awaiting surgical procedures [21]. In the context of end-stage liver disease, its primary goal is to counteract progressive sarcopenia and frailty, which significantly affect perioperative outcomes.

The analyzed studies demonstrate considerable heterogeneity in prehabilitation interventions, including differences in program structure, intensity, and the level of patient supervision. Despite this, common components can be identified. The key element of prehabilitation remains structured physical training, typically performed 2–3 times per week, including both aerobic exercise (e.g., walking, cycle ergometer training) and resistance training aimed at improving muscle strength [8]. In some studies, interventions were extended to include nutritional support, highlighting the multimodal nature of this approach [6,11].

The duration of prehabilitation programs most commonly ranged from 6 to 12 weeks, corresponding to the waiting period for liver transplantation and representing a potential therapeutic window for intervention. However, an important limitation observed in these studies was low patient adherence to exercise recommendations, which affects the interpretation of intervention effectiveness.

The assessment of prehabilitation outcomes was based on objective measures of physical performance and frailty. The most commonly used parameters included peak oxygen consumption ( $\text{VO}_{2\text{peak}}$ ), 6-minute walk distance (6MWD), daily step count, handgrip strength, and the Liver Frailty Index (LFI).

### Results of Studies on Prehabilitation

#### Physical Performance

The analyzed interventional studies demonstrated that prehabilitation programs are associated with improvements in physical performance parameters in patients awaiting liver transplantation. The most commonly observed effects included an increase in the distance covered during the 6-minute walk test (6MWT) and an increase in daily physical activity levels, measured by step count [5,6].

In some studies, improvements in parameters of maximal aerobic capacity were also reported, including an increase in  $\text{VO}_{2\text{peak}}$  during exercise testing [5,8]. This suggests that prehabilitation may positively influence both functional capacity and maximal exercise performance.

However, it should be emphasized that the magnitude of the observed effect varied across studies. These differences may result from the heterogeneity of interventions (differences in intensity, duration, and type of training), as well as from the small sample sizes of the analyzed groups.

Based on the available data, it can be concluded that prehabilitation leads to improvements in physical performance parameters; however, the strength of evidence remains limited [5,6,8,10].

#### Clinical Outcomes

Data regarding hard clinical endpoints remain significantly limited. In the study by Morkane et al., a statistically significant reduction in length of hospital stay after liver transplantation was demonstrated, whereas the analysis by Al-Judaibi et al. showed only a trend toward shorter hospitalization and fewer 90-day readmissions, without reaching statistical significance [8,9].

For other endpoints, such as mortality and the incidence of postoperative complications, there is a lack of clear evidence confirming the benefits of prehabilitation. Currently available data suggest a potentially favorable impact of prehabilitation on selected clinical outcomes; however, their quality and sample sizes do not allow for definitive conclusions.

A summary of the key studies is presented in Table 1.

**Table 1.** Characteristics of the key studies evaluating the impact of prehabilitation in liver transplant candidates.

| Author (year)              | Duration                                 | Population   | Results                                                                                                      |
|----------------------------|------------------------------------------|--------------|--------------------------------------------------------------------------------------------------------------|
| Debette-Gratien et al. [5] | 12 weeks                                 | 13 patients  | Increase in $\text{VO}_{2\text{peak}}$ , 6minute walk distance, and knee extensor strength.                  |
| Serper et al. [6]          | 14 weeks                                 | 30 patients  | Increase in daily step count.                                                                                |
| Wallen et al. [7]          | 8 weeks                                  | 38 patients  | Confirmation of the safety and feasibility of the training program in this population.                       |
| Morkane et al. [8]         | 6 weeks                                  | 33 patients  | Increase in $\text{VO}_{2\text{peak}}$ and reduction in length of hospital stay after liver transplantation. |
| Al-Judaibi et al. 2019 [9] | Waiting period for liver transplantation | 458 patients | Lower rate of 90-day readmissions and shorter length of hospital stay (without statistical significance).    |
| Williams et al. 2019 [10]  | 12 weeks                                 | 18 patients  | Improvement in physical performance (ISWT) and physical function (SPPB).                                     |
| Skladany et al. 2023 [11]  | 3 months                                 | 80 patients  | After 1 month, an improvement in LFI was observed in the prehabilitation group.                              |
| Loschi et al. 2025 [12]    | 12 weeks                                 | 57 patients  | Improvement in the Liver Frailty Index.                                                                      |



### 5. Limitations of the Current Evidence

A significant limitation of the analyzed studies is the level of patient adherence to prehabilitation programs. Studies in which prehabilitation was conducted in hospital settings under medical supervision demonstrated higher adherence compared to home-based programs

[7].

Another important limitation is the heterogeneity of the interventions, including differences in the type of exercises performed, their intensity, and the duration of prehabilitation programs. This makes direct comparison between studies difficult and limits the ability to draw definitive conclusions.

The duration of prehabilitation programs may also be a limiting factor. Given the progressive nature of ESLD and the relatively short waiting time for transplantation in some patients, the time available for intervention may be insufficient to induce meaningful physiological adaptations that translate into improved clinical outcomes.

An additional limitation is the small sample sizes and the lack of large randomized controlled trials, which affects the overall quality of the available evidence.

These factors indicate the need for further research in this area, particularly to standardize prehabilitation interventions and to obtain more robust and conclusive results.

### 6. Discussion

Despite the growing number of studies on prehabilitation in patients awaiting liver transplantation, current knowledge in this area remains limited. In particular, there is a lack of large randomized controlled trials that would allow for a clear assessment of the impact of prehabilitation on hard endpoints such as mortality and postoperative complications. An important issue that may explain the discrepancy between improvements in functional parameters and the lack of clear impact on hard clinical outcomes is the multifactorial nature of perioperative risk in patients with ESLD. While prehabilitation targets physical capacity, outcomes such as mortality and postoperative complications are also strongly influenced by factors including liver disease severity, portal hypertension, nutritional status, and comorbidities. Therefore, isolated improvement in physical performance may be insufficient to significantly modify these complex endpoints.

An important direction for future research is the standardization of prehabilitation programs, including the determination of the optimal type of exercise, its intensity, frequency, and duration. The current heterogeneity of interventions significantly hampers the comparison of results across studies.

Another key aspect is the identification of patient groups that derive the greatest benefit from prehabilitation, particularly in relation to the severity of frailty and the stage of liver disease.

An important implication of the available evidence is that prehabilitation should not be limited to physical training alone but rather implemented as a multimodal intervention. Given the underlying pathophysiology of ESLD, including hypercatabolism, sarcopenia, and metabolic disturbances, optimization of nutritional status may play a critical role in supporting anabolic processes and enhancing the effects of exercise-based interventions.

In addition, psychological support may be relevant, as patients awaiting liver transplantation often experience anxiety, depression, and reduced motivation, which can negatively affect adherence to prehabilitation programs [22]. Addressing behavioral factors, including smoking and alcohol use, may further contribute to improving overall physiological reserve and perioperative outcomes.

Therefore, future prehabilitation models should incorporate structured nutritional, psychological, and behavioral interventions as standard components, rather than optional adjuncts.

In the future, the development of home-based or telemedicine-supported prehabilitation models may also be important, as they could increase accessibility and improve patient adherence to recommended interventions.



## 7. Conclusions

Prehabilitation represents a promising strategy for preparing patients for liver transplantation, aimed at improving physical performance and reducing the severity of frailty.

Available data indicate that prehabilitation interventions may lead to improvements in functional parameters such as VO<sub>2</sub>peak and the distance covered in the 6-minute walk test, as well as contribute to better overall functional status.

At the same time, it should be emphasized that the impact of prehabilitation on hard endpoints, including mortality and the incidence of postoperative complications, remains inconclusive and requires further investigation.

Given its low risk and potential benefits, prehabilitation may constitute a valuable component of pre-transplant preparation, particularly in patients with frailty and reduced physical performance.

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