Title:
PHYSICAL FRAILTY IN LIVER TRANSPLANTATION

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Physical frailty in liver transplantation

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ABSTRACT

In patients with cirrhosis, frailty represents a status of global physical dysfunction associated with a multiplicity of factors, including muscle wasting, undernutrition and malnutrition, and functional impairment. This condition is particularly prevalent among those with advanced cirrhosis, such as liver transplant (LT) candidates. Studies in this
vulnerable population have demonstrated that its presence is independently predictive of adverse outcomes both pre- and post-transplantation, and thus that its incorporation into clinical practice could result in improved clinical decision-making, particularly regarding the identification of candidates for physical and nutritional interventions. There are, however, some limitations to its immediate incorporation into organ allocation prioritization models, including the wide heterogeneity of instruments used for measuring frailty, and particularly the lack of a single one suitable in all LT clinical scenarios (inpatient vs outpatient; pre-vs post-transplant). Finally, the data on the potential effects of frailty improvement on the diverse range of outcome measures are still preliminary.

**Keywords:** Frailty. Sarcopenia. Cirrhosis. Liver transplantation.

**INTRODUCTION**
Currently, most liver transplant (LT) centers prioritize organ allocation based on the Model for End-Stage Liver Disease (MELD) score, with or without the addition of serum sodium concentration (MELDNa). This system, which determines the severity of disease in subjects with cirrhosis from serum total bilirubin, creatinine, and international normalized ratio (INR) values using a logarithmic mathematical formula (1), has been widely recognized for its objectivity, fairness, and success in reducing mortality on LT waiting lists (2). Spain is the country with the highest donation rate in the world, and with optimal waiting times, mortality, and list drop-offs when compared to those observed in other countries. Despite this, in 2019 there were 3% of deaths (n = 45) and 5% (n = 85) of drop-outs, in the context of worsening clinical condition and/or development of contraindications, of a total of 1,686 waitlisted adults (3). These data suggest that factors other than MELD should be considered into the decision-making process regarding prioritization for liver transplantation. In fact, similar changes are occurring in donor and recipient profiles, with an increase in those considered to be older (> 60 yrs), with frequent metabolic comorbidities, and in the case of recipients an increase in non-alcoholic steatohepatitis etiology (3). In a sense, the new phenotype of the typical LT candidate is that of a sicker, medically and
particularly metabolically more complex, and “frail,” patient (4). The main aim of this review is to provide an update on the evidence that links frailty to pre- and post-transplant outcomes.

**FRAILTY AND CIRRHOSIS**

In geriatrics, where the relevance of frailty was first assessed, it is defined as “a state of increased vulnerability to physical stress (i.e., surgery) and decreased physiologic reserve” (5). This situation, described by Fried et al., included sarcopenia (decreased skeletal muscle mass), progressive immobility, decreased energy expenditure, and malnutrition (6). We now envision it as a multidimensional concept where multiple systems and organs are compromised (cardiovascular, neurologic, endocrine, musculoskeletal systems), including the very relevant psychosocial component of the condition (4).

Frailty is a novel concept in the hepatology field due to its high prevalence in LT candidates and impact on outcome both pre- and post-LT. Overall, it is estimated that 20% of candidates are frail, with an additional two in five in a pre-frail status based on data collected using the Fried frailty instrument (5). Most of the focus is on physical frailty, related to functional impairment, that is, loss of the ability to perform everyday activities and maintain health/wellness, and therefore excluding other relevant cognitive, social, or emotional factors that are more difficult to objectively measure (4). Sarcopenia is the main component of frailty in LT candidates. The concept of frailty, though, is more than a simple loss of muscle mass; it describes a situation of global physical dysfunction that also includes parameters of functional performance and capacity (7).

In LT candidates, physical frailty is influenced by many factors, including liver disease severity, age, muscle mass, nutritional status, and non-liver related comorbidities (diabetes, heart disease, kidney failure, etc.) (5). While in some individuals the influence of some non-liver factors is relatively small, and their outcome is well reflected by the MELD score, in others the presence of comorbidities, malnutrition, and sarcopenia has substantial prognostic value, sometimes even higher than severity of liver disease. Indeed, patients with the same MELD score are highly heterogeneous.
in terms of clinical phenotype, clinical manifestations, sense of acuity and outcome, as reflected by the degree of frailty these patients display. The integration of frailty into clinical practice is difficult due to lack of consensus on its definition, assessment tools, and implications for decision-making concerning LT prioritization (8).

TOOLS TO ASSESS PHYSICAL FRAILTY

Subjective methodology
In the process of initiating a LT evaluation and deciding to waitlist a patient, there is undoubtedly a subjective part (9). The clinician’s assessment (i.e., the “eye-ball test”, the Clinical Frailty Scale or Braden’s Scale) has been shown to predict waitlist mortality in patients with cirrhosis (10). Unfortunately, this is a subjective method susceptible of inter-observer variability, and unless proven to be as effective as other objective measurements, we should not be using it for such important decisions.

Objective methodology
Several instruments can be used to objectively assess frailty in patients with cirrhosis (Table 1).
Sarcopenia, a component of frailty, can be measured using different methods to quantify muscle mass, including anthropometry, bioimpedance, densitometry, ultrasound, or cross-sectional imaging tests such as computed tomography (CT) scans or magnetic resonance imaging (MRI) (7).

The North American group of experts in sarcopenia advocates for the use of CT-based skeletal muscle area, measured at the third lumbar vertebra on an abdominal CT scan, using a body segmentation software (e.g., ImageJ, sliceOmatic) (7,11) and gender-specific skeletal muscle index (SMI) cut-off values (SMI < 50 cm²/m² in men and < 39 cm²/m² in women) (12). It provides a more precise measurement than the psoas muscle index (PMI), especially in men with cirrhosis (13). It can be easily incorporated into clinical practice given that cross-sectional imaging tests are routinely used in pre-transplant evaluation, and it is a cheaper and more widely available test compared to MRI-based imaging (14). Whether changes over time such as the delta MELD are more sensitive, or whether calculating the psoas muscle as opposed to total muscle area is
better, is still an area of ongoing research (7).

In order to understand the impact that these anatomical changes, together with additional ones that take place during the course of advanced chronic liver disease, have on a patient’s physical functionality, different tests are also available. Self-reported tests (Activities of Daily Living [ADL], Instrumental Activities of Daily Living [IADL], Karnofsky Scale [KPS]) or performance-based tests (Fried frailty instrument, Short Physical Performance Battery [SPPB], six minute walk distance [6MWD] or gait speed) have shown to be useful in predicting mortality in LT candidates (15). The new Liver Frailty Index is a continuous index, easily performed in clinical practice, that is specific for patients with cirrhosis. It consists of three simple, performance-based tests: a) dominant grip strength measured by a dynamometer (in kilograms); b) chair-stands (time in seconds that it takes for a patient to stand up and sit down in a chair five times without using the arms); c) balance, which is the patient’s ability of holding three positions balance during ten seconds (side, semi-tandem, and tandem) (16). For frailty classifications, previously established cut-offs are used to define “robust” (< 3.2), “pre-frail” (between 3.2 and 4.1) and “frail” (≥ 4.2) (16,17). An on-line calculator is available (https://liverfrailtyindex.ucsf.edu/).

These physical tests may be affected by some circumstances or intermediate events such as large-volume ascites, thereby nor correctly reflecting the true functional capacity of the patient. In fact, most of these have been investigated in the outpatient setting, where patients are in a relatively “stable” clinical situation. Among patients with refractory ascites, the low scores obtained with these tests have been shown to reflect their scarce muscle mass and deficient nutritional status, rather than an incapacity to follow the test instructions (15,16).

**Evidence for their use in clinical practice**

According to the North American expert opinion statement on frailty in LT, every patient with cirrhosis awaiting LT should undergo a frailty assessment both at baseline and longitudinally using a standardized frailty instrument (4).

Indeed, there is no evidence supporting a single frailty tool as suitable for frailty assessment in all clinical settings related to LT: inpatient vs outpatient or pre-
transplant vs post-transplant. Considering the need for objectivity, speed, and low-cost, frailty experts selected a “4-tool battery” (KPS, ADL, 6-MWT and Liver Frailty Index), which would be selected depending on each patient’s clinical scenario, available resources, and the clinical decision to be made based on tests results (4).

In the outpatient clinic, the Liver Frailty Index is the instrument with the widest experience and applicability in LT candidates. It is objective, easy to use, and may be repeated longitudinally. In turn, the measurement of SMI on an abdominal CT scan is possibly the test to use for hospitalized patients in whom performance-based frailty assessments may be compromised due to acute changes in functional performance, and therefore may not appropriately reflect the underlying physiological reserve in a clinically stable situation (Table 2).

OUTCOME MEASURES BASED ON FRAILTY

There is an abundance of recent data, including large prospective studies, pointing towards an adverse effect of frailty on pre- and post-transplant outcome measures.

In the pre-LT setting, frailty has been shown to be associated with:

1. Decreased quality of life (18,19) and increased risk of depression (20).
2. Increased rate of liver-related complications and length of hospital stay (21-25).
   For instance, sarcopenia is an independent risk factor for hepatic encephalopathy (26). Other complications such as ascites and infections are also more frequent in sarcopenic than in non-sarcopenic cirrhotic patients (27).
3. Increased morbidity and mortality rates on the waitlist, regardless of liver disease severity (5,16,23,28-32).

In the post-LT setting, frailty has been shown to be associated with: a) a higher probability of death (33); b) an overall increase in rate of complications (34,35), particularly infections (27,36); c) a longer duration of hospital and Intensive Care Unit (ICU) stay (27,37,38); d) higher overall healthcare costs (39); e) an increased need for a rehabilitation center at discharge (40); and f) a greater risk of persistent post-LT frailty phenotype (41).

While the data regarding the pre-LT setting is strong and quite conclusive, the impact on post-LT outcome measures is less robust, as it is mostly based on retrospective
investigations. Limitations and controversial findings are very likely related to the high heterogeneity found in the instruments used to assess frailty, the inclusion of both in- and out-patients, and the fact that most investigations are US-based, single-center studies (8).

**APPROACH AND UTILITY IN CLINICAL PRACTICE**

**Prognostic factor guiding clinical decision-making regarding transplant urgency**

The MELD score has proven its predictive capacity in a wide variety of patients with cirrhosis awaiting LT. Indeed, its implementation led to reductions in waitlist time and waitlist deaths (42,43). Unfortunately, MELD incorporates into its formula serum creatinine, which is not only dependent on renal function (as a surrogate of the hemodynamic changes observed in the advanced cirrhotic patient with portal hypertension) but also on muscle mass; frailty/sarcopenia might thus potentially penalize patients, limiting their access to LT with the current prioritization system, as it was proven to be the case with women. Furthermore, MELD does not incorporate any nutritional or functional status variables (29). This may in fact be the reason for the low ability of MELD score to predict survival following LT (44). A frailty-based score would allow for an indirect measurement of the weight of the extra-hepatic manifestations of cirrhosis (malnutrition and functional decline) as well as of co-morbidities not related to liver disease (age, diabetes, heart disease, etc.), thus becoming a very useful predictor of outcome. It is important to highlight that a single frailty assessment should never be the only reason for not including or removing a patient from the LT waitlist, since there is no evidence to support a specific frailty cut-off beyond which a person should not undergo LT (4). A patient’s frailty status should be combined with additional objective criteria (medical, functional or psychosocial) to determine transplant candidacy and transplant urgency, thus complementing MELD score. Indeed, adding frailty/sarcopenia to the MELD score improves prediction of mortality in patients with cirrhosis, mainly in those with low MELD scores, who are the most disadvantaged by the current prioritization system (17,29). Studies investigating modifications of the MELD score where serum creatinine is replaced by a parameter not influenced by muscle mass should also be promoted (Fig. 1).
Prognostic factor guiding physical interventions

The different components of frailty, sarcopenia, malnutrition, and physical function are potentially reversible with nutritional and physical interventions (45). Longitudinal measurement of frailty can be used to identify the best timing for referral of a pre-frail patient to a specific physical and nutritional intervention, as well as to select those who would benefit from a post-transplant rehabilitation program (Fig. 1) (15).

“Pre-habilitation” refers to a multidisciplinary approach (incorporating physical and nutritional training) aimed at enhancing a patient’s physiological reserve prior to surgery (4,46). Several pre-habilitation programs, including comprehensive physical activity programs, home-based supervised exercises, educational and lifestyle interventions, and/or nutritional advice, have been shown to improve results and decrease the cost of abdominal surgery (4). In the LT setting, the impact of pre-habilitation programs has been studied in small, single-center cohorts but with equally good results (46-48). In a pilot study, LT candidates were involved in an intensive aerobic exercise program, highlighting that these types of program are feasible and possibly beneficial for improving fitness in patients with advanced liver disease (48).

Expert consensus documents have incorporated algorithms to tailor pre-habilitation intensity to frailty status in the LT candidate. In moderately and severely frail patients, the experts recommend waiting for 2-4 weeks and 4-12 weeks, respectively, before considering their waitlist inclusion or reactivation while interventional strategies are implemented (Fig. 1) (4). Regarding post-transplant rehabilitation, LT surgery itself leads to a deterioration of functional capacity. This functional capacity takes time to recover (31), and when recovered, it remains below predictive values (49). Furthermore, it has been shown that muscle fatigue may become a chronic problem that further reduces physical activity post-LT (50). In a Spanish single-center study, the authors evaluated changes in maximal strength, aerobic capacity, and health-related quality of life in LT recipients after a combination of supervised resistance and aerobic training; they observed a significant improvement in physical condition (47). In summary, while data are still scarce, they do point to the importance of incorporating
longitudinal frailty measurements in clinical practice when designing specialized care plans including both pre-habilitation programs prior to LT and post-transplant physical recovery programs.

One of the key points for success in such programs is the incorporation of transplant staffers, particularly nurses, who would be in charge of frailty assessments before and after LT, as well as of direct and tight collaboration with Primary Health Care practitioners and the patient’s family environment, taking into consideration their socioeconomic and cultural level.

CONCLUSIONS

In the cirrhotic population several circumstances contribute to frailty, including malnutrition, muscle wasting, and functional decline.

Frailty is a predictor of adverse outcomes in the LT setting; there is robust evidence that it predicts pre-transplant mortality independent of the severity of liver disease. Although less robust, data pointing towards its impact in post-transplant outcome measures are also available. Well-designed, prospective multi-center studies in this area are underway to better understand the effect on post-transplant outcome.

The wide range of instruments used for measurement limit the incorporation of frailty into routine clinical practice. In the outpatient setting, the Liver Frailty Index is considered as the most easily applicable and reliable tool. In the in-patient setting, SMI measurement on an abdominal CT scan has the broadest applicability among all frailty-assessing tools.

Objective frailty assessment should be incorporated into clinical practice as: a) a prognostic factor guiding clinical decision-making regarding transplant urgency; and b) an intervention tool to identify candidates for habilitation programs before or even after LT. A single frailty assessment should never be the only criterion for not including or removing a patient from the LT waitlist but should be handled as one of many objective criteria routinely considered when determining transplant candidacy. Frailty could be considered as another vital sign that is measured longitudinally during routine clinical visits with the necessary involvement of transplant nurses.
Some questions still remain that need further research in the field, including the impact of frailty status on mortality following LT, the impact of longitudinal changes in frailty status on LT outcomes, and the relationship between frailty and liver disease progression, if any.

REFERENCES
8. Lai JC. Advancing adoption of frailty to improve the care of patients with cirrhosis: time for a consensus on a frailty index. Am J Gastroenterol 2016;111(12):1776-7. DOI: 10.1038/ajg.2016.485


<table>
<thead>
<tr>
<th>Type of measurement</th>
<th>Frailty tools</th>
<th>Characteristics</th>
</tr>
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<tbody>
<tr>
<td><strong>Anatomical measures</strong></td>
<td>Muscle mass (sarcopenia)</td>
<td><strong>Anthropometry (7)</strong></td>
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<td></td>
<td></td>
<td><strong>Bioimpedance (7)</strong></td>
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<td></td>
<td></td>
<td><strong>Densitometry (7)</strong></td>
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<td></td>
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<td><strong>Cross-sectional imaging tests (CT/MRI)</strong></td>
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<td><strong>Functional measures</strong></td>
<td>Capacity for physical performance</td>
<td><strong>Self-reported tests</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>Performance-based</strong></td>
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<tr>
<td>Performance-based</td>
<td>+ exhaustion + weight loss</td>
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<tr>
<td>Performance-based</td>
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<tr>
<td>Tests</td>
<td>Description</td>
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<td>----------------------------------------------------------------------</td>
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<tr>
<td>Physical inactivity + weakness + slowness + exhaustion + weight loss</td>
<td>Physical inactivity + weakness + slowness + exhaustion + weight loss</td>
<td></td>
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<tr>
<td>Short Physical Performance Battery (15)</td>
<td>Balance + chair stand + gait speed</td>
<td></td>
</tr>
<tr>
<td>Six Minute Walk Distance (15)</td>
<td>Distance covered by walk in 6 minutes</td>
<td></td>
</tr>
<tr>
<td>Liver Frailty Index (16,17)</td>
<td>Grip strength + chair stands + balance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Specific for cirrhosis</td>
<td></td>
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<tr>
<td>Performance-based tests</td>
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BMI: body mass index; CT: computed tomography scan; MRI: magnetic resonance imaging.
Table 2. Selection of frailty instruments and frailty staging criteria depending on clinical setting in patients with cirrhosis

<table>
<thead>
<tr>
<th>Frailty tools</th>
<th>Stages of frailty</th>
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<tr>
<td></td>
<td>Severe</td>
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<tr>
<td><strong>Outpatient</strong></td>
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<td>Performance-based tests</td>
<td></td>
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<tr>
<td>Liver Frailty Index (16,17)</td>
<td>≥ 4.2</td>
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<tr>
<td>Six Minute Walk Distance (4,15)</td>
<td>&lt; 250 meters</td>
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<tr>
<td><strong>Inpatient</strong></td>
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<tr>
<td>Self-reported tests</td>
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<tr>
<td>Activities of Daily Living (ADL) (4,15)</td>
<td>Difficulty with ≥ 2 ABVD</td>
</tr>
<tr>
<td>Karnofsky Scale (4,15)</td>
<td>≥ 0-40</td>
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<tr>
<td>Abdominal CT scan</td>
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<tr>
<td>Skeletal muscle index measured at the third lumbar vertebra (7,11,38)</td>
<td>Men &lt; 50 cm²/m²</td>
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</table>
*Adapted from Lai JC et al., Am J Transplant 2019 (4). CT: computed tomography.
PHYSICAL FRAILTY

PROGNOSTIC FACTOR
(complementary to MELD score)

INTERVENTION tool

Periodic frailty assessment while on the waitlist

Waitlist PRIORITIZATION

MILD frailty

MODERATE/SEVERE frailty

Optimization of PHYSICAL and NUTRITIONAL status

Identification and monitoring of pre-habilitation candidates

Yes

Waitlist PRIORITIZATION

No

Waitlist EXCLUSION (futility)*

Reversibility/Stabilization of frailty status during waitlist follow-up
(every 2-4 weeks if severe; every 4-12 weeks if moderate)

LT as usual
Fig. 1. Utility of frailty in routine clinical practice regarding liver transplantation (LT). *The decision not to transplant due to patient frailty status requires multidisciplinary discussion, and must always be reassessed longitudinally.