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PHYSICAL FRAILTY IN LIVER TRANSPLANTATION

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REVIEW

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, under 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

**Abbreviations**
LT: Liver Transplantation; MELD: Model for End-Stage Liver Disease; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; SMI-L3: Skeletal Muscle Index measured at the third lumbar vertebra; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; KPS: Karnofsky Scale; SPPB: Short Physical Performance Battery; 6-MWD: Six Minute Walk Distance; LFI: Liver Frailty Index

**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 with optimal waiting times, mortality and drop-offs from the lists compared to those observed in other countries. Despite it, in 2019, there were 3% of deaths (n=45) and 5% (n=85) of drop-outs in the context of clinical condition worsening and/or development of contraindications of a total of 1686 waitlisted adults [3]. These data suggest that factors other than MELD should be considered into the decision-making process regarding prioritizing for liver transplantation. In fact, similar changes are occurring in the donor and recipient profiles, with increases of those considered older (> 60 yrs), with frequent metabolic comorbidities and in case of the 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” [4]. The main aim of this review is to provide an update of 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 and cols 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) including the very relevant psychosocial part of it [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 2 in 5 in a prefrail status based on data 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, 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...) [5]. While in some, 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 have substantial prognostic value, sometimes even higher than that of the severity of the liver disease. Indeed, patients with the same MELD score are highly heterogeneous in terms of clinical phenotype, clinical manifestations, sense of equity and outcome, reflected by the degree of frailty of these patients. Integration of frailty into clinical practice is difficult due to the lack of consensus on its definition, assessment tools and
implications for decision-making on LT prioritization [8].

TOOLS TO ASSESS PHYSICAL FRAILTY

Subjective methodology
In the process of initiating a LT evaluation and deciding to list a patient, there is undoubtedly a subjective part [9]. The clinician assessment (i.e., the ‘Eye ball test’, the Clinical Frailty Scale or the Braden Scale) has been shown to predict waitlist mortality in patients with cirrhosis [10]. Unfortunately, this is a subjective method subjected to 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 scan –CT- 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 < 50cm²/m² in men and < 39cm² /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 is more sensitive or whether calculating the psoas muscle as opposed to the total muscle area are still areas of 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 the patient 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: (i) dominant grip strength measured by a dynamometer (in kilograms); (ii) chair-stands (time in seconds) that it takes for a patient to stand up and sit down in a chair 5 times without using the arms; (iii) balance which is the patient’s ability of holding 3 positions balance during 10 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 online 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 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 versus post-transplant. Considering the need for objectivity, speed and low-cost, the frailty experts selected a “4-tools battery” (KPS, ADL, 6-MWT and Liver frailty index) which would be selected depending on the patient's clinical scenario, available
resources, and the clinical decision to be made based on the tests results [4].

In the outpatient clinic, the Liver frailty index is the instrument with the wider experience and applicability in LT candidates. It is objective, easy to use and repeat longitudinally. In turn, measurement of SMI on an abdominal CT scan is possibly the test to use in 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 patients’ physiological reserve in a clinical stable situation (Table 2).

**OUTCOME MEASURES BASED ON FRAILTY**

There is abundance of recent data, including large prospective studies, pointing towards an adverse effect of frailty of pre and posttransplant outcome measures. *In the pre-LT setting*, frailty has been shown to be associated with (i) decreased quality of life [18-19] and increased risk of depression [20]; (ii) 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]; and (ii) increased morbidity and mortality rate on the waitlist independent of liver disease severity [5, 16, 23, 28-32].

*In the post-LT setting*, frailty has been shown to be associated with (i) a higher probability of death [33], (ii) overall increased rate of complications [34-35], particularly infections [27, 36], (ii) a longer duration of hospital and intensive care unit (ICU) stay [27, 37-38], (iv) higher overall healthcare costs [39]; (v) an increased need of a rehabilitation center at discharge [40] and (vi) a greater risk of persistent postLT frailty phenotype [41].

While the data from the preLT setting is strong and quite conclusive, the impact on postLT 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 of instruments used to assess frailty, the inclusion of both in and out-patients, and the fact that most are single US based center studies [8].
PROGNOSTIC FACTORS AND UTILITY IN CLINICAL PRACTICE

Prognostic factor guiding clinical decision-making regarding transplant urgency

The MELD score has proven its prediction capacity along a wide variety of patients with cirrhosis awaiting LT. Indeed, its implementation led to reductions in waitlist time and deaths on the waitlist [42-43]. Unfortunately, MELD incorporates into its formula serum creatinine, which is not only dependent on renal function (as a surrogate of haemodynamic changes observed in the advanced cirrhotic patient with portal hypertension) but also on muscle mass; frailty/sarcopenia might thus potentially penalize patients limiting the access to LT with the current prioritization system, as it has proven to happen with women. Furthermore, MELD does not incorporate any nutritional nor functional status variables [29]. This may in fact be the reason for the low ability of the 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 co-morbidities not related to the 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]. The patient’s frailty status should be combined with additional objective criteria (medical, functional or psychosocial) to determine transplant candidacy and transplant urgency complementary to the 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 the patient’s muscle mass should also be promoted (Figure 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 to refer 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 (Figure 1) [15]. “Pre-habilitation” refers to a multidisciplinary approach (incorporating physical and nutritional training) aimed at enhancing the patients’ 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 shown to improves results and decrease the costs of abdominal surgeries [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 programs are feasible and possibly beneficial at improving fitness in patients with advanced liver disease [48]. Expert consensus documents have incorporated algorithms to tailor pre-habilitation intensity to the frailty status of the LT candidate. In moderately and severely frail patients, the experts recommend to waiting 2-4 weeks and 4-12 weeks, respectively, before considering their waitlist inclusion or reactivation, while interventional strategies are implemented (Figure 1) [4]. Regarding post-transplant rehabilitation, LT surgery itself leads to a deterioration of patients’ 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 the data are still scarce, it does point to the importance of incorporating longitudinal frailty measurements in clinical practice to design specialized care plans including both pre-habilitation programs prior LT and post-transplant physical recovery programs.

One of the key points for success of such programs is the incorporation of transplant staff, particularly nursing, who would be in charge of frailty assessments before and after LT as well as direct and tight collaboration with primary health care
and the patients’ 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 outcome in the LT setting; there is robust evidence that it predicts pre-transplant mortality independent of the severity of the liver disease. While less robust, there is also data pointing towards its impact in post-transplant outcome measures. Well designed, prospective multi-center studies in this area are underway to better understand the effect on posttransplant outcome. The wide range of instruments used for its measurement limit its incorporation into routine clinical practice. In the outpatient setting, the Liver Frailty Index is considered the most easily applicable and reliable tool. In the in-patient setting, the SMI measurement on an abdominal CT scan has the broadest applicability among all the frailty tools. Objective frailty assessment should be incorporated into clinical practice as (i) a prognostic factor guiding clinical decision-making regarding transplant urgency, and (ii) an intervention tool to identify candidates for habilitation programs before or even after LT. A single frailty assessment should never be the only criteria 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 clinic visits with the necessary involvement of transplant nursing. Some questions still need for further research in the field, including the impact of frailty status on mortality following LT, the impact of longitudinal changes in frailty status in LT outcomes and the relationship between frailty and liver disease progression.

REFERENCES


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# Table 1: Objective tools to measure physical frailty

<table>
<thead>
<tr>
<th>TYPE OF MEASUREMENT</th>
<th>FRAILTY TOOLS</th>
<th>CHARACTERISTICS</th>
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<tbody>
<tr>
<td><strong>ANATOMICAL measures</strong></td>
<td></td>
<td></td>
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<tr>
<td>Muscle mass (sarcopenia)</td>
<td>Anthropometry&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Size, Weight, BMI, Tricipital fold, Mid-arm and calf circumference.</td>
</tr>
<tr>
<td></td>
<td>Bioimpedance&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Lean mass + fat mass + Fat body mass index + Phase angle</td>
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<td></td>
<td>Densitometry&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Lean and fat mass indices</td>
</tr>
<tr>
<td></td>
<td>Cross-sectional imaging tests (CT*/ MRI**)</td>
<td>Individual Psoas muscle measurement</td>
</tr>
<tr>
<td></td>
<td>Psoas muscle area&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psoas thickness&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Transversal diameter measured at the level of the umbilicus.</td>
</tr>
</tbody>
</table>
|                                            | Skeletal muscle index<sup>11,12</sup> | Sum of the area of all skeletal muscles at the level of the third or fourth vertebra.
| **FUNCTIONAL measures**                    |                                    |                                                                                 |
| Capacity for physical performance          | Activities of Daily Living<sup>15</sup> | Daily self-care activities                                                      |
|                                            | Instrumental Activities of Daily Living<sup>15</sup> | Activities let an individual live independently                                 |
|                                            | Karnofsky Scale<sup>15</sup>       | Physical activity                                                               |
|                                            | Fried frailty instrument<sup>6,15</sup> | Physical inactivity + weakness + slowness + exhaustion + weight loss             |
|                                            | Short Physical Performance Battery<sup>15</sup> | Balance + chair stand + gait speed                                               |
|                                            | Six Minute Walk Distance<sup>15</sup> | Distance covered by walk in 6 minutes                                            |
|                                            | Liver Frailty Index<sup>16,17</sup> | Grip strength + chair stands + balance. Specific for cirrhosis.                 |

* Computed Tomography scan. **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></th>
<th>FRAILTY TOOLS</th>
<th>STAGES OF FRAILTY</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td>OUTPATIENT</td>
<td>Performance-based tests</td>
<td>≥ 4,2</td>
</tr>
<tr>
<td></td>
<td>- Liver frailty index\textsuperscript{16,17}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Six Minute Walk Distance\textsuperscript{4,15}</td>
<td>&lt; 250 meters</td>
</tr>
<tr>
<td>INPATIENT</td>
<td>Self-reported tests</td>
<td>Difficulty with ≥ 2ABVD</td>
</tr>
<tr>
<td></td>
<td>- Activities of Daily Living (ADL)\textsuperscript{4,15}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Karnofsky Scale\textsuperscript{4,15}</td>
<td>0-40</td>
</tr>
<tr>
<td></td>
<td>Abdominal CT\textsuperscript{**} scan</td>
<td>Men &lt; 50cm\textsuperscript{2}/m\textsuperscript{2}</td>
</tr>
<tr>
<td></td>
<td>- Skeletal muscle index measured at the third lumbar vertebra\textsuperscript{7,11,38}</td>
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* Adapted from Lai AmJTransplant 2019; ** Computed Tomography
Figure 1: Utility of frailty in routine clinical practice regarding liver transplantation (LT)

* The decision not to transplant due to the patient frailty status requires multidisciplinary discussion and it must always be reassessed longitudinally.