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## Defining the Threshold for Too Sick for Transplant

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### Abstract

**Purpose of review**—The most difficult – and perhaps, most important – decision that a clinician makes for a patient on the liver transplant wait-list is when *not* to proceed with liver transplant. While an individual may be suitable for transplant surgery at listing, he may become too sick while waiting.

**Recent findings**—This article reviews four specific conditions that commonly arise on the wait-list that may render a candidate too sick for transplant: advancing age, sarcopenia, acute on chronic liver failure, and non-liver-related medical comorbidities. Each condition, *per se*, is often not a criterion for delisting; the challenge arises when conditions exist in combination – how does one “sum” up these conditions to quantify risk? Physical frailty, conceptually, represents the conditions in a candidate that are unlikely to reverse after liver function returns, or will take so long to reverse that the patient will be highly vulnerable to post-operative complications. Pre-transplant assessments of physical frailty, which are objective, easily administered and repeated in the clinical setting, enable us to measure the extent to which these factors – in isolation or combination – will reduce both quantity and quality of life after liver transplant.

**Summary**—In this article, I introduce a framework that incorporates objective pre-transplant assessments of physical frailty to facilitate the decision regarding when a patient is too sick for transplant.

### Keywords

frailty; sarcopenia; post-transplant mortality; wait-list mortality; older adult

### Introduction

Half a century after Dr. Thomas Starzl performed the first human liver transplant, liver transplantation has become a well-accepted treatment option for patients with end-stage liver disease. The decision to list a patient for liver transplant is now standardized and straightforward. In general, a patient with an indication for transplant (e.g., decompensated cirrhosis, hepatocellular carcinoma), adequate social support, well-controlled medical comorbidities, and absence of active substance use is eligible for listing. But the condition of a transplant candidate is dynamic; although an individual may be suitable for transplant surgery at listing, s/he may become too sick while waiting. There is little consensus, however, on when *not* to proceed with transplantation, and as a result, this threshold for “too

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sick” varies by patient, provider, and program. This chapter discusses specific conditions that emerge in candidates after listing that commonly raise concerns by transplant teams regarding transplant suitability. I will then provide a framework for making this high-stakes decision to proceed – or not – with liver transplant surgery.

## Specific conditions that commonly arise on the wait-list that may render a candidate too sick for transplant (Table 1)

### Advanced and advancing age

A quarter of liver transplant candidates spend over four years on the wait-list;<sup>10</sup> a patient listed at the age of 63 years, considered relatively young, may age into a senior citizen while on the list. Older age has repeatedly been associated with worse pre- and post-transplant outcomes,<sup>2,11,12</sup> despite selection bias towards listing and transplanting only the “healthiest” of older patients. Candidates ≥65 years compared to <65 years experience a 35% increased odds of death or delisting for being too sick for transplant and 9% decreased odds of transplant (Table 1).<sup>1</sup> This is likely because older adults are particularly vulnerable to developing conditions during the wait to transplant that make it more challenging to achieve a favorable transplant-related outcome. For example, among older candidates (≥65 years), poor physical function is an important prognostic factor, associated with a nearly 3-fold increased odds of wait-list mortality compared to physically robust candidates <65 years (OR 2.7, 95%CI 1.4–5.2).<sup>13</sup> After transplant, older *recipient* age is associated with an increasing adjusted risk of graft loss (Table 1).<sup>2</sup> There exists a powerful interaction between age and laboratory MELD score at the time of transplant. At high MELD scores, defined as >28, liver transplant recipients between 65–69 years and ≥70 years (compared to <60 years) experienced significantly increased risk of graft loss (for 65–69 years: HR 1.4, 95%CI 1.2–1.7; for ≥70 years: HR 2.4, 95%CI 1.7–3.3) [p=0.01 for the interaction between age and laboratory MELD at transplant].<sup>14</sup> Furthermore, the development of pre-transplant diabetes or need for mechanical ventilation prior to transplant are associated with poor outcomes after transplant among older recipients,<sup>11</sup> and should be considered factors that make an *older* adult too sick for liver transplant. Clearly, ongoing assessment of transplant suitability as older candidates age further on the wait-list is warranted.

### Sarcopenia

Sarcopenia is a term that refers to severe loss of muscle mass.<sup>15</sup> Most commonly quantified by abdominal skeletal muscle area on cross-sectional imaging, sarcopenia has been reported in 38–66% of patients with cirrhosis.<sup>16–19</sup> Pre-transplant sarcopenia is strongly associated with transplant-related outcomes. In a study of 142 liver transplant candidates, sarcopenia was associated with an over 2-fold increased hazard of mortality, adjusted for MELD and age (Table 1).<sup>3</sup> After liver transplant, every 1000 mm<sup>2</sup> increase in skeletal muscle area of the psoas at the 4<sup>th</sup> lumbar vertebra was associated with a 73% decreased risk of mortality [n=163 liver transplant recipients; Table 1].<sup>4</sup> Post-transplant survival among liver transplant recipients with the highest compared to lowest quartiles of total psoas muscle area were 87% and 50% at 1-year and 77% and 26% at 3-years.<sup>4</sup> Using low body mass index as an approximation of sarcopenia, liver transplant recipients with a body mass index (BMI) <18.5 kg/m<sup>2</sup> (n=863) experienced a higher risk of death (HR 1.4; 95%CI 1.2–1.7) and graft loss

(HR 1.3; 95%CI 1.1–1.5) compared to recipients with a BMI of 18.5–24.9 kg/m<sup>2</sup>.<sup>20</sup> Given significantly inferior outcomes among liver transplant candidates and recipients with low muscle mass, sarcopenia should be considered a criterion for being too sick for transplant.

### **Acute on chronic liver failure (ACLF)**

ACLF is defined as “a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterized by acute hepatic decompensation resulting in liver failure and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from onset”.<sup>21</sup> In the absence of transplant, mortality at 28 and 90 days increases with grade of ACLF: 22% and 41% for ACLF Grade 1, 32% and 52% for ACLF Grade 2, and 77% and 79% for ACLF Grade 3.<sup>5</sup>

Early transplant, defined as within 28 days of ACLF onset, is associated with significantly improved survival compared to those who did not receive transplant, with a probability of 1-year survival after transplant of 75% compared to 10% survival without transplant ( $p<0.001$ ).<sup>6</sup> However, the presence of multi-organ failure and associated infections that constitute this clinical syndrome often render a patient too sick for transplant.

### **Medical co-morbidities**

Pre-existing medical conditions that are unrelated to the underlying liver disease will not improve, and may even worsen, after liver transplant. Such conditions include coronary artery disease, diabetes, peripheral arterial disease, hyperlipidemia, and chronic obstructive pulmonary disease (COPD). Unfortunately, due to selection of recipients with only well-controlled conditions, our ability to assess the impact of specific pre-existing non-liver-related conditions on post-transplant outcomes is limited and the data are conflicting. In a study of U.S. liver transplant recipients from 2002–2006, obesity, defined as a BMI>35 kg/m<sup>2</sup>, was the only pre-existing condition that was associated with post-transplant mortality (Table 1).<sup>7</sup> Diabetes, COPD, peripheral arterial disease, angina, or coronary artery disease were not. In a separate study utilizing the United Kingdom national liver transplant registry, only cardiovascular disease was identified as a risk factor for long-term mortality after liver transplant (Table 1).<sup>8</sup> Similar to the US cohort, diabetes, COPD, chronic renal insufficiency, or connective tissue disease did not emerge as predictors of mortality.<sup>8</sup> However, in a single center study (n=624) that evaluated more granular-level data on medical co-morbidities, coronary artery disease, diabetes, COPD, and chronic renal insufficiency were each associated with an increased adjusted risk of mortality after liver transplant (Table 1).<sup>9</sup> Given the conflicting results between data from large administrative databases versus the smaller but more granular single center cohort, better methods to assess the impact of pre-existing medical co-morbidities on transplant-related outcomes are needed.

### **Pre-transplant assessment of transplant suitability**

While we might all agree that these conditions raise concerns about a candidate’s suitability for transplant surgery, each condition – in isolation – is often not sufficient to overcome the enormous pressure to proceed with transplantation from the patient, caregivers, and

transplant team that accumulates with time on the wait-list. How does one “sum” the above conditions to determine whether a patient has reached the threshold of being too sick for transplant?

One answer lies in the assessment of physical frailty. Originally developed in the field of geriatrics, “frailty” is a biological syndrome of increased vulnerability to stressors that predisposes patients to adverse health outcomes including frequent hospitalizations, institutionalization, and ultimately, death.<sup>22,23</sup> While many tools have been developed in geriatric cohorts to capture various aspects of physical frailty, all measures have the common goal of *objectively* identifying the external manifestation of this vulnerability. Several of these tools, the Fried Frailty Index, Short Physical Performance Battery, six-minute walk test, and Activities of Daily Living scale, have been studied in patients with end-stage liver disease and demonstrate construct validity and prognostic value (Table 2).

How do assessments of physical frailty allow us to identify who is too sick for transplant beyond liver disease severity alone? Complications of cirrhosis and portal hypertension undoubtedly contribute to physical frailty. Indeed, higher MELD scores and higher rates of ascites and hepatic encephalopathy are observed in frail compared to non-frail liver transplant candidates.<sup>23,24</sup> But, as clinicians, we have all seen end-stage liver disease physically impact patients in very different ways that are not reflected by their MELD score or simply by the presence of ascites. Conceptually, tools to objectively measure physical frailty allow us to quantify *the extent to which* complications of cirrhosis negatively impact outcomes. For example, a physically robust candidate who decompensates after a variceal bleed will be able to be quickly extubated after endoscopy, recover from acute on chronic liver failure, and be eligible for transplant. A frail candidate with the same complication may find himself with ventilator-dependence from aspiration pneumonia, ileus (from prolonged immobility), then with refractory encephalopathy (from inability to administer lactulose) – and be unsuitable.

Perhaps more importantly, objective assessments of physical frailty allow us to measure the extent to which extra-hepatic comorbidities, such as advancing age and diabetes, will impact outcomes. This is critical, as medical co-morbidities *unrelated* to the underlying liver disease will persist, if not worsen, after liver transplant. For example, advancing age, in and of itself, may not present as physical frailty – we have all seen a number of “youthful” 75 year olds. But a 75-year old with diabetes requiring insulin and coronary artery disease requiring intervention is likely to manifest at least some degree of physical inactivity, weakness, slowed gait or difficulty with chair stands (i.e., components of the frailty measures) that represent his increased vulnerability to adverse post-transplant outcomes. Add advanced sarcopenia, and he is at high risk for a complicated post-operative course that will severely reduce his quality of life, if not survival, after transplant.

## **Framework for determining the threshold for “too sick for transplant” (Figure)**

While there are no absolute criteria for the threshold for “too sick for transplant”, I propose a framework, incorporating pre-transplant assessments of physical frailty, to identify patients

who will not achieve optimal outcomes after liver transplant (Figure). In this framework, pre-transplant assessments of physical frailty represent the components that are unlikely to reverse after liver function returns (e.g., autonomic dysfunction from long-standing diabetes) – or will take so long to reverse (e.g. sarcopenia) that the patient will be highly vulnerable to post-operative complications such as poor wound healing, hospital-acquired or opportunistic infections. Candidate A, who is physically robust and, therefore, has sufficient physiological reserve to withstand surgery, will achieve rapid return to full function and enjoy long survival and high quality of life. Candidate B, who is physically “pre-frail”, may experience several hospital readmissions and require institutionalization after discharge for rehabilitation. However, with careful optimization of certain transplant factors (e.g., transplant at a low MELD score, use of a high quality donor), Candidate B can ultimately achieve a favorable outcome. Candidate C, who is physically frail, has so little physiologic reserve that even in the most optimal of transplant circumstances is at high risk for a complicated post-operative course that will impair his ability to achieve a high quality of life after transplant and reduce his survival. It is this patient, Candidate C, who is too sick for transplant.

## Conclusion

The most challenging – and perhaps, the most important – decision that a transplant clinician makes is when *not* to proceed with liver transplant. While it is a highly individualized decision, pre-transplant assessments of physical frailty can help us identify the combination of factors that will not reverse after transplant and therefore increase a patient’s vulnerability to adverse post-transplant outcomes. We can then incorporate these assessments into the conceptual framework proposed in this paper. This framework can be used not only to facilitate our decision about whether or not to proceed with transplant, but also to facilitate the discussion with our patients about what liver transplant can reasonably achieve.

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None

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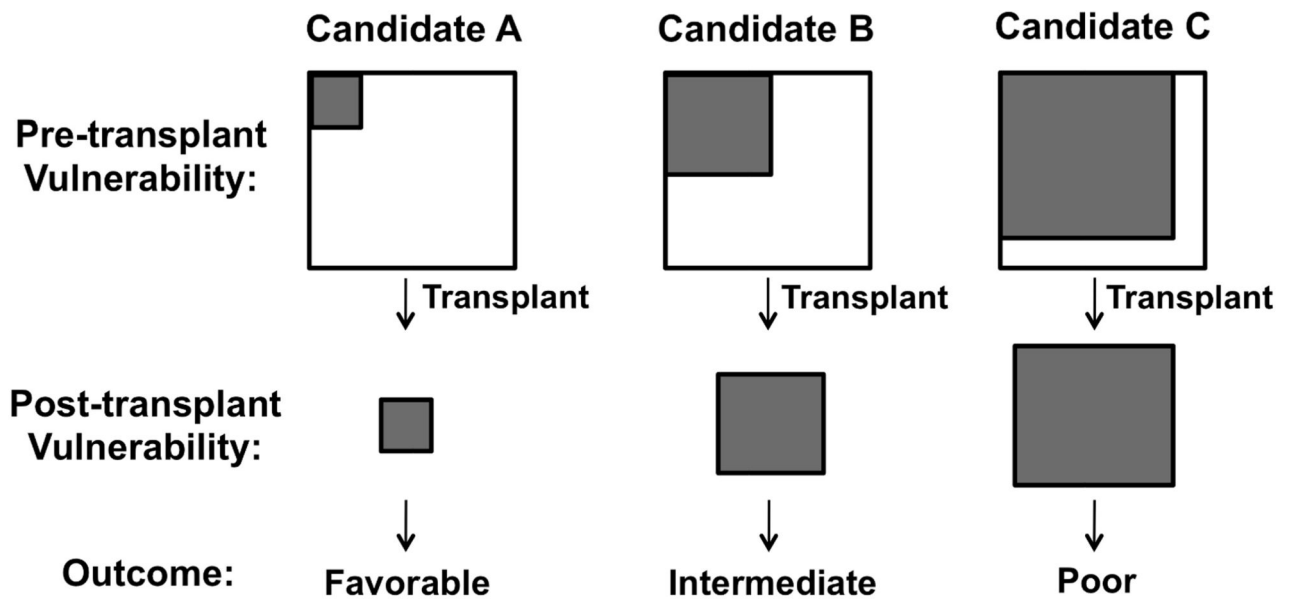
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**KEY POINTS**

- There is little consensus on when *not* to proceed with liver transplant, and as a result, the threshold for “too sick” varies by patient, provider, and program.
- Advancing age, sarcopenia, acute on chronic liver failure, and non-liver-related medical co-morbidities are common conditions that arise while on the wait-list that can render a patient too sick for transplant.
- Objective assessments of physical frailty enable us to evaluate the extent to which pre-transplant conditions will impair both quality of life and survival after liver transplant.
- A framework that incorporates pre-transplant assessments of physical frailty to identify those patients who are highly vulnerable to adverse outcomes after transplant can facilitate the decision regarding whether a patient is too sick for transplant.



**Figure.** Framework for evaluating who is "too sick to transplant". (Adapted from Flint et al<sup>27</sup>)

**Table 1**

Specific conditions that commonly arise on the wait-list that may render a candidate too sick for transplant

Condition	Definitions	Increased risk of adverse pre- and post- transplant outcomes
<b>Advanced/advancing age</b>	Over age 65 years	<ul style="list-style-type: none"> <li>Increased odds of wait-list mortality for candidates ≥ 65 years (compared to &lt;65 years): OR 1.35 (95% CI, 1.29–1.41)<sup>1</sup></li> <li>Decreased odds of liver transplant for age ≥ 65 years (compared to &lt;65 years): OR 0.91 (95% CI, 0.88–0.95)<sup>1</sup></li> <li>Increased adjusted hazard of graft loss for recipients age 65–69 years (compared to 50–54 years): HR 1.43 (95% CI 1.32–1.54) and for recipients age ≥ 70 years: HR 1.72 (95% CI 1.53–1.93)<sup>2</sup></li> </ul>
<b>Sarcopenia</b>	Severe loss of muscle mass as measured by skeletal muscle area	<ul style="list-style-type: none"> <li>Increased adjusted hazard of wait-list mortality among candidates with sarcopenia (versus non-sarcopenic): HR 2.4 (95% CI 1.2–4.5)<sup>3</sup></li> <li>Decreased hazard of death after transplant for every 1000 mm<sup>2</sup> increase in psoas muscle area: HR 0.27 (95% CI 0.47–0.86)<sup>4</sup></li> </ul>
<b>Acute on chronic liver failure</b>	Acute hepatic decompensation in the setting of chronic liver disease/cirrhosis that results in liver failure and one or more extra-hepatic organ failures	<ul style="list-style-type: none"> <li>Pre-transplant: 28-day mortality=34% and 90-day mortality=51%<sup>5</sup></li> <li>Liver transplant within 28 days of presentation of ACLF was associated with 75% one-year survival<sup>6</sup></li> </ul>
<b>Medical co-morbidities</b>	Any medical condition not directly associated with end-stage liver disease including diabetes, coronary artery disease, chronic obstructive pulmonary disease	<ul style="list-style-type: none"> <li>Increased hazard of post-transplant mortality associated with: <ul style="list-style-type: none"> <li>BMI&gt;35 kg/m<sup>2</sup> HR 1.2 (95% CI 1.0–1.4)<sup>7</sup></li> <li>Cardiovascular disease: HR 1.6 (95% CI 1.2–2.2)<sup>8</sup></li> <li>Coronary artery disease: HR 2.3 (95% CI 1.3–4.3)<sup>9</sup></li> <li>Diabetes: HR 1.4 (95% CI 1.0–1.9)<sup>9</sup></li> <li>COPD: HR 1.7 (95% CI 1.1–6.5)<sup>9</sup></li> <li>Chronic renal insufficiency: HR 1.6 (95% CI 1.2–2.3)<sup>9</sup></li> </ul> </li> </ul>

Table 2

Tools to measure physical frailty, physical function, or disability in patients with end-stage liver disease and their prognostic value.

Measure <sup>ref</sup>	Brief description of the measure	n	Median laboratory MELD	Rates of frailty	Outcomes	Associations with outcomes
<b>Fried Frailty Index</b> <sup>24</sup>	Consists of unexplained weight loss, exhaustion, physical inactivity, gait speed, grip strength	294 liver transplant candidates with MELD $\geq 12$	15	17% with Fried Frailty Index $\geq 3$	Death or delisting for being too sick for transplant	HR 1.45 (95% CI, 1.04–2.02) per 1 point increase
<b>Short Physical Performance Battery (SPPB)</b> <sup>24</sup>	Consists of gait speed, timed chair stands, and balance			27% with SPPB < 10		HR 1.19 (95% CI, 1.07–1.32) per 1 point decrease
<b>6 minute walk test (6MWT)</b> <sup>25</sup>	Record distance walked in 6 minutes	121 liver transplant candidates	17	12% with 6MWT distance < 250 meters	Death	HR 0.58 (95% CI, 0.37–0.93) per 100m increase in 6MWT distance
<b>Activities of Daily Living (ADL)</b> <sup>26</sup>	Assesses ability to feed, bathe, dress, toilet, and transfer.	734 cirrhotics admitted to the hospital (1358 times)	18	31% with need for assistance with 1 ADL	90-day mortality	OR 1.83 (95% CI, 1.05–3.20) for ADL < 12 (out of 15)
					Discharge to rehabilitation hospital	OR 3.78 (95% CI, 1.97–7.29) for ADL < 12 (out of 15)