



Review

Frailty and Sarcopenia as Routine Pre-Transplant Predictors: Moving Beyond MELD-Based Risk Assessments

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Abstract

The MELD-based scoring system is the most important tool to date for liver transplant allocation. It is useful as an index of the severity of the disease, but not a true measure of functional capacity, physiologic reserve or of the wider implications of end-stage liver disease. Frailty and sarcopenia have gained attention as important prognostic markers that provide information beyond traditional laboratory tests. This narrative review examines current evidence on the role of frailty and sarcopenia in liver transplant candidates. Focus is placed on waitlist mortality, post-transplant outcomes, and potential implications for decision-making. Studies evaluating the Liver Frailty Index (LFI), radiologic measures of sarcopenia and associated outcomes in patients with cirrhosis were reviewed. The LFI is a commonly used measurement of frailty. It is linked with increased risk of waitlist mortality even after adjusting for current MELD-based allocation models, ascites and hepatic encephalopathy. Frailty has been demonstrated not to be fixed and even modest gains are associated with reductions in mortality. Liver transplantation should not be precluded only based on frailty, as liver transplant recipients experience a survival benefit across the full spectrum of frailty severity. There is also a strong correlation between sarcopenia, myosteatosis and poor outcomes such as increased waitlist and post-transplant mortality; complications and prolonged hospital stay. Frailty and sarcopenia are closely related and when taken together, they give a better overall picture than either measure alone. Frailty and sarcopenia are complementary predictors of outcomes in liver transplant candidates, addressing important gaps in MELD-based allocation models. Incorporating performance and body composition measures into pre-transplant evaluation may improve prognostic accuracy, help identify patients for prehabilitation and support a better approach to patient assessment and management.

Keywords: frailty; sarcopenia; liver disease; cirrhosis; MELD; liver transplant; prehabilitation



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1. Introduction

The Model for End-Stage Liver Disease (MELD) and its derivatives remain central to liver transplant allocation due to their objectivity and reproducibility. MELD was originally derived to predict short-term mortality in cirrhosis and has consistently demonstrated strong discrimination for 90-day outcomes [1,2]. However, its reliance on laboratory parameters limits its ability to capture broader aspects of patient health, particularly functional status and physiologic reserve.

This limitation has become increasingly evident as transplant populations have evolved. Patients with similar scores on current MELD-based allocation models scores often demonstrate markedly different risks of waitlist mortality and post-transplant recovery. Severe hypoalbuminemia, hepatorenal syndrome, and hepatic hydrothorax are significant events that independently predict increased mortality, even after accounting for current MELD-based allocation models [3–5]. These complications identify a patient subgroup with high short-term mortality that may be overlooked by MELD-based systems and hence MELD exception points may be granted depending on specific criteria. This indicates the limitation of MELD based scoring and its derivatives, that is its inability to capture the full impact of systemic manifestations of advanced cirrhosis.

Frailty and sarcopenia have emerged as key constructs that explain this heterogeneity. Both reflect systemic consequences of cirrhosis, including muscle wasting, inflammation, and metabolic dysfunction, and provide prognostic information that extends beyond biochemical liver function. The pathophysiological mechanisms linking cirrhosis to sarcopenia and frailty are multifactorial, encompassing hyperammonemia, endotoxemia, cytokine release, insulin resistance, and gut dysbiosis, all of which contribute to anabolic resistance and progressive functional decline [6].

The prognostic significance of these parameters is substantial. A large meta-analysis demonstrated that pre-liver transplant sarcopenia is associated with a significantly increased risk of post-transplant mortality and morbidity [7]. Another meta-analysis focusing on opportunistic computed tomography screening found that patients with muscle mass loss diagnosed by the Psoas Muscle Index method had a 4.1 times higher risk of death after transplantation compared to non-sarcopenic patients [8]. Malnutrition is associated with increased mortality in cirrhosis, and its prognostic impact appears stronger in advanced disease and transplant-listed populations compared with unselected cirrhosis cohorts [9]. These findings underscore that conventional liver biochemistry does not capture the full spectrum of disease burden in cirrhosis, and that systematic assessment of muscle mass and physical function should be integrated into routine pre-transplant evaluation to improve risk stratification and guide targeted prehabilitation interventions.

2. Methods and Literature Review

A literature search was conducted using PubMed/MEDLINE for studies published up to June 2026. Search terms included combinations of frailty, Liver Frailty Index, Clinical Frailty Scale, Model for End-Stage Liver Disease score (MELD score), MELD-Na score, MELD-3.0 score, sarcopenia, myosteatosis, muscle wasting, cirrhosis, end-stage liver disease, liver transplantation, waitlist mortality, post-transplant outcomes, and prehabilitation. Reference lists of relevant articles, systematic reviews, meta-analyses, and society guidance documents were also screened to identify additional studies.

Preference was given to prospective cohorts, multicenter studies, systematic reviews, meta-analyses, and practice guidance involving adults with cirrhosis undergoing transplant assessment or transplantation. Studies evaluating validated frailty measures, particularly the Liver Frailty Index, and imaging-based assessments of sarcopenia and myosteatosis were prioritized. Articles were selected based on their clinical relevance, methodological rigor, and contribution to understanding outcomes not fully explained by conventional liver disease severity scores.

Because of the differences in the study populations, assessment methods, and reported outcomes; findings were synthesized narratively. Studies that assessed the prognostic value of frailty and sarcopenia beyond current MELD-based scoring systems and other known markers of disease severity were given special consideration. No formal risk-of-bias assessment was performed as this was a narrative review, but larger studies, multicenter

cohorts and evidence supported by systematic reviews or meta-analyses were given more weight. Evidence was synthesized narratively because of substantial heterogeneity in study design, frailty assessment tools, sarcopenia definitions, imaging methodologies, outcome measures, and statistical approaches. Given the narrative nature of this review, a formal risk-of-bias assessment was not performed. Greater emphasis was placed on high-quality evidence, including multicenter prospective cohorts, systematic reviews, meta-analyses and major hepatology guidance documents. Studies focused exclusively on pediatric populations, non-cirrhotic liver disease, publications without clear outcome data, or publications lacking sufficient methodological detail were excluded.

There are a number of important limitations to the evidence available. Many of the publications are based on observational studies, which are prone to residual confounding and cannot prove causality. Many studies are based in transplant centers and selected waitlist populations, which may not be representative of the general population of cirrhosis patients. Additionally, there are differences in the tools used to assess frailty across studies, and the definitions of sarcopenia vary, as do thresholds for muscle mass loss and myosteatosis. Furthermore, there is limited interventional data regarding the impact of targeted nutritional, exercise, or prehabilitation strategies on transplant-related outcomes. This review is a narrative synthesis of the literature and was not intended as a systematic review or meta-analysis. The aim was to give a clinically relevant update on the current evidence on frailty and sarcopenia in chronic liver disease. It is meant to highlight where measures of sarcopenia and frailty overlap with usual prognostic tools and to discuss implications for clinical practice and future research.

3. Frailty in Cirrhosis: Definition and Clinical Relevance

Frailty represents a state of reduced physiologic reserve and increased vulnerability to stressors. The term frailty in the context of cirrhosis refers to something more specific than just physical decline. A state in which physiologic reserve has been depleted so that even mild stressors such as infection, procedure or a fall, can cause disproportionate deterioration [10,11]. This vulnerability is usually brought about by three mechanisms: sarcopenia (loss of muscle mass required to cope with catabolic stress); impaired energy metabolism (liver's reduced ability to store and mobilize glycogen); and chronic low-grade inflammation (maintenance of a catabolic state in the body despite the patient's apparent clinical stability). All these processes work together. A patient with advanced liver disease is likely to be losing muscle mass and not using available nutrients appropriately, while systemic inflammation is still destroying tissue at a greater rate than it is being repaired. This gives rise to a phenotype that is not reflected in standard liver-specific scores, which are based on laboratory parameters and organ function.

The Liver Frailty Index (LFI), which incorporates grip strength, chair stands, and balance testing, has been specifically developed and validated in this population [12,13]. Each assesses a different functional decline: grip strength as a proxy for overall sarcopenia, chair stands as a measure of lower extremity power and ability to perform activities of daily living, and balance testing as a measure of neuromuscular coordination that determines fall risk. One of the reasons for the popularity of the tool is its usability. It only takes about 5 min, is not too complicated to set up, and can be administered by clinic staff. That simplicity is clinically important. Even if a frailty measure has excellent predictive properties on paper, it is unlikely to be used routinely in a busy hepatology clinic if it requires sophisticated equipment or lengthy protocols.

In a landmark multicenter cohort of 1044 liver transplant candidates across nine U.S. centers, frailty defined by $LFI \geq 4.5$ was present in approximately 25% of patients [10]. There were also significant numbers of patients with decompensating events: 36% with

ascites and 41% with hepatic encephalopathy. These are not just side notes. The presence of ascites and hepatic encephalopathy were both established markers of hepatic decompensation and the study showed that patients with either complication had significantly higher odds of meeting the criteria for frailty than those without. Is the LFI measuring something different from decompensation, or is it just another symptom of the same underlying disease severity? The mortality data indicate the former. Patients who were also frail had a waitlist death rate of 29%, nearly double that of non-frail patients with ascites (17%). The same trend was observed for hepatic encephalopathy; with a 30% mortality rate for frail patients compared to 20% for non-frail patients with the same complication. That is, frailty was not just tracking with disease severity, but stratifying risk within patients with similar levels of decompensation.

The adjusted analysis makes the case more direct. In univariable models, ascites, hepatic encephalopathy, and frailty were each independently associated with waitlist mortality. However, the inclusion of all three variables in a single model at the same time resulted in only frailty remaining statistically significant. Although ascites and hepatic encephalopathy are known poor outcome predictors, they were not independent predictors after the inclusion of frailty [10]. This finding is critical: it demonstrates that frailty captures a dimension of risk that supersedes even major clinical decompensating events. This outcome is very important and one way to think of frailty is as a sort of integrative summary measure, reflecting the cumulative physiologic burden of ascites, encephalopathy, and any other subclinical processes that are depleting the patient's reserve that a list of individual complications cannot. What the data do indicate is that frailty assessment provides additional prognostic information beyond that provided by decompensating events alone, and that a patient's functional status should be considered separately in risk stratification.

The prevalence and clinical impact of frailty have been confirmed in larger, more diverse cohorts. In a prospective study of 1108 candidates across multiple transplant centers, frailty was associated with approximately a twofold increase in waitlist mortality, independent of body mass index and MELD-Na [14]. This study stratified patients by obesity status and found that the association between frailty and waitlist mortality increased progressively with higher body mass index. Among patients without obesity, the adjusted hazard ratio for waitlist mortality associated with frailty was 1.54 (95% CI 1.02 to 2.33). This increased to 1.72 (95% CI 0.99 to 2.99) among patients with class 1 obesity (BMI 30 to 34.9 kg/m²) and surged to 3.19 (95% CI 1.75 to 5.82) among patients with class 2 or higher obesity (BMI $\geq$ 35 kg/m²) [14]. These findings demonstrate that the combination of frailty and obesity confers particularly high risk, likely reflecting the phenomenon of sarcopenic obesity in which low muscle mass coexists with excess adiposity.

An important recent study from the Multicenter Functional Assessment in Liver Transplantation (FrAILT) study examined whether liver transplantation provides survival benefit across all levels of frailty [15]. Among 2628 patients in the pre-transplant cohort, 731 (28%) were frail, and 440 (17%) died before receiving a transplant. In the post-transplant cohort of 1335 patients who underwent transplantation, 325 (24%) were frail and 103 (8%) died after transplantation. The study computed restricted mean survival times and found that while pre-transplant survival decreased substantially as LFI increased, post-transplant survival decreased only modestly with increasing LFI. Critically, there was no LFI threshold at which the risk of post-transplant mortality exceeded the risk of pre-transplant mortality; patients derived net survival benefits from transplantation at all LFI values. Pre-transplant frailty was associated with increased post-transplant mortality and greater healthcare utilization after liver transplantation [15]. Even patients with advanced frailty benefit

from transplantation, and the survival benefit is driven primarily by the reduction in pre-transplant mortality risk.

Collectively, these studies underscore that frailty captures a dimension of risk not reflected by conventional clinical or biochemical parameters. The LFI is now the most extensively validated frailty tool in hepatology, with established cutoffs ($LFI \geq 4.5$ for frail, 3.2 to 4.4 for pre-frail, <3.2 for robust), demonstrated inter-rater reliability, and proven prognostic value independent of current MELD-based scoring systems. Furthermore, the demonstration that frailty may be able to be addressed, that improvements in LFI are associated with mortality benefit, and that transplantation provides survival advantage even in frail patients. These points support routine frailty assessment at initial evaluation and serially while on the waitlist.

4. Frailty Trajectory and Dynamic Risk Assessment

A single frailty score, however precisely measured, is a snapshot and this misses trajectory. This is more important in cirrhosis than in most chronic diseases, as the underlying disease does not always progress in a linear fashion. Patients can decompensate and then respond to treatment followed by stabilization and then decompensate again. A patient evaluated in a relatively good period may look much less frail than three months later, and vice versa. If frailty is considered a static characteristic, fixed at the first visit and assumed to be constant, then the very patients that are most clinically informative may be missed.

A study that looked into this question included 2851 clinic visits from 1093 outpatients with cirrhosis, which enabled the researchers to model the frailty trajectory, not just the frailty at a single time point trajectories [16]. The main result was a graded relationship between the change in frailty and waitlist mortality: the cumulative incidence of death or delisting due to being too sick increased across the increasing levels of frailty trajectories. These results support that frailty is a dynamic process of functional reserve and not a single-point-in-time classification. Importantly, worsening frailty was an independent risk factor for adverse outcomes even after adjusting for other factors. After controlling for baseline Liver Frailty Index (LFI), age, height, MELD-Na, and serum albumin, each 0.1-unit reduction in the Liver Frailty Index (LFI) per 3 months was associated with a 2.04-fold increase in the subdistribution hazard of death or delisting (95% CI, 1.35–3.09). On the other hand, those whose frailty status worsened over time were at higher risk of death or delisting. The findings as a whole suggest that the assessment of frailty should be done over time, rather than at one point in time, but do not set a threshold or an optimal time to reassess. This increase in frailty remained strongly associated and statistically significant, after adjusting for these known markers, indicating that it is reflecting a process other than the single biochemical derangements measured by the standard laboratory-based scores, likely a cumulative physical burden of repeated decompensation.

This is supported by the comparison group. Patients with a better frailty trajectory during the same follow-up period were significantly less likely to die or be delisted compared to those who remained stable or deteriorated. This symmetry, along with worsening trajectories predicting harm and improving trajectories predicting relative protection, increases confidence that the relationship is not an artifact of reverse causation. There is still some caution to be taken. No competing risk model, no matter how well it is adjusted, can completely eliminate unmeasured confounding, such as sarcopenic obesity, subclinical infection, or intermittent hepatic encephalopathy, which may not be included in the covariates listed. The data do confirm, with reasonable confidence, that frailty is not a one-time diagnosis that can be made and then forgotten. It is more like a vital sign, one that should be followed over time, and a deterioration in this is an independent indicator of risk, irrespective of the patient's MELD-based score or albumin at any particular visit.

The dose–response relationship between small improvements in frailty and reduction in mortality is important. Additionally, single frailty measurement, taken at one point in time, tells only part of the story. If a patient has moderately worse LFI and is improving over time, they are in a different risk category than a patient with the same LFI who is deteriorating over time. The evidence is from a cohort of 1029 patients who had serial LFI measurements [17]. This longitudinal tracking of frailty can enable researchers to pose a more clinically relevant question: Is the patient becoming more or less frail, and how much does this change affect survival? The reported result is that for every 0.1-point reduction in LFI over a three-month period, the risk of death while waiting for a transplant was reduced by 6%. This creates a measurable, incremental goal. This approach does not see frailty as a static characteristic that can be measured and reported, but rather as a variable that may be addressed, and that even modest improvements in physical function have a measurable impact on prognosis. The important point is not the precise percentage, but the implication: LFI is not a fixed prognosis, but a target that can shift, and shifting it, even slightly, seems to have real survival implications. This is the first time in the frailty literature that a specific, numeric target, an improvement of approximately 0.1–0.2 points over three months, can be suggested as a benchmark for prehabilitation programs. For those who are candidates for transplant, there is now a measurable target to aim for with exercise interventions, nutritional optimization, and structured physical therapy. It is not yet known if this degree of change can be achieved in all stages of cirrhosis and if the mortality advantage is maintained in all types of liver disease. The current evidence is encouraging, but not definitive about the magnitude of the benefit; however these data do provide some targets to be considered for prehabilitation interventions especially when designing future studies.

5. Impact of Frailty on Post-Transplant Outcomes

Frailty's prognostic reach does not stop once a patient receives an organ. Transplantation itself is a major physiologic insult, involving hours of surgery, substantial blood loss, and a recovery period that demands real functional reserve. A patient who enters the operation already depleted has less capacity to withstand that insult, and the data support this. A multicenter cohort of 1166 liver transplant recipients across eight U.S. centers, 21% were classified as frail before transplant using the same LFI threshold of 4.5 [15]. Cumulative incidence of death at one year was 6% among frail patients versus 4% among non-frail patients. At five years the gap widened to 16% versus 10% (log-rank $p = 0.02$). Unadjusted pre-transplant frailty was associated with a 62% increased risk of post-transplant mortality and when adjustment for body mass index, hepatocellular carcinoma status, donor age, and donation after circulatory death status was done the hazard ratio rose to 2.13. This association persisted even after adjustment for MELD-Na, age, sex, diabetes and donor risk index.

In addition to survival, perioperative complications and hospital and ICU length of stay were also significantly higher in frail recipients. Frail patients were approximately 2 times more likely to have a prolonged hospitalization, approximately 56% more likely to have a prolonged stay in the intensive care unit (ICU), and approximately 72% more likely to have 17 or more days in the hospital. They were also two and a half times more likely to be discharged away from home, which is a sign of functional dependency and has its own downstream costs. These results have implications beyond the waitlist period. They seem to reflect a physiologic susceptibility that remains after surgery and during recovery, influencing survival, hospital length of stay, and discharge disposition. The relevant question is whether intervening on frailty before transplant (prehabilitation, nutrition, or structured exercise) could reduce this gap.

Later analyses of data from the same cohort revealed a survival advantage for liver transplantation at every frailty level up to and including those with advanced frailty [18]. The question is not only if frail patients fared worse after transplant but if transplant was better than staying on the waitlist. The pre-transplant cohort consisted of 2628 ambulatory patients with cirrhosis who were awaiting transplant, excluding those with HCC; the median MELD-Na was 18, and 28% were frail, with 17% dying prior to transplant. The post-transplant cohort consisted of 1335 recipients, median MELD-Na 20, 24% frail, with 8% mortality following transplant. As LFI increased, pre-transplant restricted mean survival time decreased significantly, as previous waitlist studies had demonstrated: the sicker the patient, the sooner they die while waiting. The restricted mean survival time after transplant was also found to be decreasing with increasing LFI, although the decrease was not as large. Importantly, the authors compared these two curves over the entire range of frailty scores and did not observe any point where the two curves intersected. Pre-transplant survival was lower than post-transplant survival at all LFI values tested, even for patients with advanced frailty. Transplantation provided a net survival benefit at all levels of frailty, including the most frail patients in the cohort. The benefit was largely due to the dramatic decrease in pre-transplant mortality that transplant offers, and not because post-transplant survival was not affected by frailty; post-transplant survival did, however, decrease slightly with increasing frailty. The data reveal that this drop was never sufficient to offset the significantly higher death risk these patients were at if they stayed on the waitlist.

The clinical implication is that frailty should guide the approach to a transplant, rather than the decision to perform a transplant. For frail patients, more intensive perioperative planning, closer monitoring and structured prehabilitation to enhance functional reserve prior to surgery may be required. However, the lack of a clear LFI threshold at which waitlist survival is greater than post-transplant survival suggests that frailty should not be the only reason for exclusion. By this evidence, a patient with advanced frailty would benefit more from transplant than from further waiting, even with the increased surgical risk associated with frailty. This discovery has definite boundaries: it is only applicable to patients who were chosen for transplant and passed the surgical evaluation process already.

6. Sarcopenia as a Complementary Biomarker

Frailty and sarcopenia are related but not synonymous. Physical frailty is characterized by reduced physiological reserve and functional capacity, and is typically evaluated by testing muscle strength, mobility and physical performance. Sarcopenia is a larger muscle disease that is defined by a decrease in skeletal muscle strength and/or quantity and quality, and physical performance is an important indicator of the severity and clinical implications of sarcopenia [19]. For patients with cirrhosis, Computed Tomography (CT)-based assessment offers an objective measure of the quantity of skeletal muscle, most frequently at the third lumbar vertebral level, where the cross-sectional area of muscle is well correlated with whole-body skeletal muscle mass [20,21]. CT-derived measures should not be used interchangeably, however, as skeletal muscle index, psoas muscle index, and transverse psoas muscle thickness are different ways of measuring muscle quantity, while myosteatosis is a measure of muscle quality. Their interpretation is further influenced by sex-specific thresholds, differences in measurement and segmentation techniques, and the lack of complete standardization across centres. Therefore, the presence of low muscle quantity as defined by CT is an important aspect of sarcopenia and may be associated with physical frailty, but neither of these is simply a single anatomical measurement. Imaging-based approach may have a few advantages over performance testing: it does not require patient effort or cooperation, and sometimes it can be performed on scans already acquired

for other reasons. The association between sarcopenia and mortality in cirrhosis is not a marginal or inconsistent finding. Data have revealed that sarcopenia is linked to increased mortality in cirrhotic patients, with a risk level similar to that of frailty measures such as the LFI, which are assessed with completely different methods.

Evidence of the relationship between sarcopenia and post-transplant outcomes also comes from a systematic review and meta-analysis that included 5875 patients across 30 studies [22]. There was heterogeneity among studies but this did not prevent the association between pre-transplant sarcopenia and post-transplant mortality from being consistent enough to yield a pooled relative risk of 1.84 (95% CI 1.41 to 2.39). This estimate is similar to the near twofold mortality risk found in previous meta-analyses based on frailty measures, indicating that the two approaches to measuring the same underlying vulnerability are convergent. The fact that two different methods of measuring muscle wasting and functional decline have similar effect sizes gives some comfort that both are measuring a real biological signal and not just an artifact of the measurement method. The meta-analysis also revealed that sarcopenia was linked to increased risk of post-transplant infections, increased surgical complications, increased requirement for fresh frozen plasma transfusion, and increased length of stay in the intensive care unit, all of which have been reported in the post-transplant setting for frailty, suggesting that these two constructs are tracking similar biology, but maybe not entirely overlapping.

One of the more clinically relevant findings in this literature is the independence of sarcopenia from current MELD-based scoring systems. MELD-based scores predict mortality based on markers which do not directly reflect skeletal muscle mass. This suggests that sarcopenia reflects a component of patient risk that is not measured by these liver-specific severity scores. This has direct implications for transplant evaluation; a patient with a modest MELD-based score may have significant sarcopenia, and therefore significant risk that would not be appreciated without a specific muscle mass assessment. Although both muscle mass and functional frailty testing seem to identify the same population of high-risk patients, the clinical utility of muscle mass will likely remain as an adjunct to functional frailty testing until muscle mass is standardized across centers.

In addition to muscle mass loss, the quality of the muscle tissue has become an important prognostic factor. Pathological fat infiltration into skeletal muscle (myosteatorsis) can be identified by reduced radiodensity of the muscle on computed tomography (CT) images [23]. In a meta-analysis of 28 studies with 7068 patients, pre-transplant myosteatorsis was identified as an independent risk factor for mortality after transplantation with a HR of 1.69 [24]. Patients with myosteatorsis also had significantly longer ICU stay, longer hospital stay, and were at significantly higher risk for post-transplant complications than those without myosteatorsis.

Frailty and sarcopenia are not identical. Frailty is a measure of functional performance and sarcopenia is a measure of body composition. In general, their modest correlation indicates that their use together would provide a more comprehensive assessment of physiologic reserve [25]. A prospective cohort study showed that insulin-like growth factor-1 levels in patients with sarcopenia were significantly lower and correlated with the Liver Frailty Index [26]. This suggests a common pathophysiologic mechanism between the two involving the growth hormone–insulin-like growth factor pathway. The rate of muscle loss over time also is very critical; among patients on transplant waiting list, a rate of muscle wasting of 1% or more per month was linked with significantly higher 1-year post-transplant mortality when compared with slower rates of muscle wasting [27].

7. Integrating Frailty and Sarcopenia into Clinical Practice

The Liver Frailty Index (LFI) is a widely used and validated frailty index in cirrhosis [19]. It can be administered in an outpatient clinic with basic bedside tests of balance, chair stands, and grip strength. The score has meaningful cutoffs which are easily understood and reproducible. This would allow it to be applicable in daily clinical practice during evaluations of transplant candidates and in follow-up of patients on the transplant waiting list. Multiple other frailty scores are available each with its own advantages and limitations [28]. The Clinical Frailty Scale (CFS) can also be carried out quickly and has been proven to have a good prognosis value in various liver disease populations [29]. In hospitalized patients with liver cirrhosis the in-hospital mortality rate was significantly higher in patients with a higher frailty category compared to those with a lower category [30]. The scale has also been linked to the risk of hepatic encephalopathy, hospital admissions and mortality; indicating that frailty screening can identify vulnerable patients who may otherwise appear stable by basic laboratory parameters [28,31].

Frailty and sarcopenia are frequently used interchangeably as two terms for the same wasting process. The relationship is more related but distinct; they are independent but synergistic risk factors. A study specifically developed to investigate both constructs together, together with resting energy expenditure, clarifies where the overlap ends [32]. The study prospectively included 97 patients with cirrhosis and portal hypertension and measured sarcopenia by transversal psoas muscle thickness normalized to height, frailty and resting energy expenditure by indirect calorimetry. The prevalence of sarcopenia (26%) and frailty (40%) immediately suggests that these are not just two terms for the same phenomenon, as the overlap between the two groups would presumably be much more complete if they were. The two groups were similar in most characteristics, except that patients with sarcopenia had a significantly lower median BMI (23 versus 28 kg/m²) and were much more likely to be hypermetabolic (60% versus 0% in frail but not sarcopenic patients). This is not a trivial distinction. It proposes that sarcopenia in this population may be at least partially attributed to a higher metabolic rate than caloric intake, which is not measured by frailty testing. A patient may be frail because of decreased activity and generalized weakness without being hypermetabolic, and sarcopenia, at least in some patients, seems more specifically related to a metabolic derangement in which the body is using muscle protein at a faster rate.

The clinical implications of this distinction are evident in the survival data. The median transplant-free survival was 3.6 months in patients with sarcopenia, 4.5 months in patients with frailty, and 10.3 months in patients without sarcopenia or frailty. These numbers would be enough to consider either of these findings as a serious prognostic marker by itself. However, patients with both sarcopenia and frailty had a worse outcome than those with either condition alone, with a median transplant-free survival of only 1.8 months which was highly significant. This is the finding that makes it possible to consider frailty and sarcopenia as synergistic. The combination resulted in a result that was significantly worse and that was consistent with two partially distinct pathophysiological processes structural muscle loss and functional decline, both of which independently contributed to the risk of death.

After adjusting for other predictors of death or transplant, sarcopenia was an independent predictor, along with hepatic encephalopathy and MELD-based score. This indicates that sarcopenia was not just a proxy for frailty, and that the effect of sarcopenia would not be eliminated once frailty was statistically removed. It had its own independent prognostic value.

These findings together suggest a practical recommendation: frailty assessment should be part of the initial transplant evaluation, providing a functional baseline for future

assessment, and repeated at intervals thereafter, based on the longitudinal frailty data presented here. However, sarcopenia and frailty seem to reflect at least partially different biological processes, one more structural and one more functional and perhaps with different underlying causes. Using frailty testing alone may lead to the exclusion of patients who are most vulnerable to muscle loss but not to overall functional decline. The two assessments, not either alone, seem to be the best at identifying the patients at truly highest risk, who had the shortest transplant-free survival in this cohort by a wide margin. If cross sectional imaging is available, which it usually is in patients with cirrhosis and ongoing follow-up, then imaging the third lumbar vertebral level should be used in conjunction with functional testing for sarcopenia. Evaluating both functional performance and muscle mass provides a better picture of physiologic reserve. This combined approach can guide prehabilitation strategies and nutritional intervention, which MELD-based scoring alone cannot do.

To facilitate clinical application, Table 1 summarizes the principal tools used to assess frailty and sarcopenia in liver transplant candidates, including commonly used thresholds, advantages, limitations and potential clinical implications. Acute decompensation, hepatic encephalopathy, hospitalization, ascites, and patient cooperation or ability to perform performance-based testing may influence individual frailty scores. Results should be interpreted in the context of the patient's clinical state rather than as fixed scores. These measures should be interpreted alongside MELD-based scores and the overall clinical context, with emphasis on identifying opportunities for prehabilitation, nutritional optimization, rehabilitation, and perioperative planning.

It is important to note that the evidence base for prehabilitation in cirrhosis remains limited, and the support for prehabilitation is therefore indirect. It derives from the prognostic monitoring literature, which establishes that frailty is dynamic and that change over time carries prognostic weight. The discussed findings provide a measurable target for prehabilitation programs, but they do not establish that such programs can achieve this target or that doing so improves outcomes. The magnitude of benefit from prehabilitation and clear patient subgroups most likely to respond to interventions still remain undefined. This distinction matters for clinical practice and for the design of future studies.

Table 1. Clinical assessment of frailty and sarcopenia in liver transplant candidates. Abbreviations: LFI—Liver Frailty Index; CFS—Clinical Frailty Scale; CT—computed tomography; SMI—skeletal muscle index; HU—Hounsfield units; SMR—skeletal muscle radiodensity.

Construct Assessed	Recommended Tool/Measurement	Suggested Timing	Commonly Used Cutoff(s)	Principal Advantage(s)	Major Limitation(s)	Potential Clinical Response
Frailty/functional reserve	Liver Frailty Index (LFI): grip strength, chair stands, and balance testing	At initial transplant evaluation and repeated longitudinally while on the waiting list; reassess when clinical status changes	LFI ≥ 4.5: frail; 3.2–4.4: prefrail; <3.2: robust [12]	Brief, inexpensive, feasible in routine clinical practice, and provides prognostic information beyond MELD-Na	Represents a time-dependent snapshot of functional status; results may be influenced by acute illness, encephalopathy, ascites, and ability to perform the tests	Risk communication; prehabilitation; structured exercise/physical therapy; nutritional intervention; perioperative planning and monitoring; serial reassessment to identify improvement or deterioration
Global frailty/vulnerability	Clinical Frailty Scale (CFS)	During initial review and when clinically indicated, particularly when performance-based testing is impractical	CFS > 4 has been used to define frailty in cirrhosis cohorts; however, thresholds vary across studies [29]	Rapid, simple bedside assessment that can complement performance-based measures and capture broader vulnerability	More subjective than performance-based testing and may be influenced by the patient's current clinical condition, including acute decompensation	Risk communication; identification of patients who may benefit from rehabilitation, nutritional support, enhanced perioperative planning, and closer monitoring
Skeletal muscle quantity/sarcopenia	Computed Tomography (CT)-based skeletal muscle index (SMI) at third lumbar vertebral level (L3) [20]	Opportunistically using abdominal CT obtained during transplant evaluation; repeat assessment as appropriate	SMI $< 50 \text{ cm}^2/\text{m}^2$ in men and $<39 \text{ cm}^2/\text{m}^2$ in women has been proposed [20]	Objective, reproducible; L3 muscle area correlates with whole-body skeletal muscle mass. CT usually available during transplant evaluation does not require patient effort	Lack of standardization across studies regarding vertebral level, muscles, segmentation and thresholds; muscle quantity does not directly measure strength/function	Nutritional optimization, resistance exercise/prehabilitation, enhanced perioperative risk stratification and supportive care, with monitoring of muscle loss or recovery
Skeletal muscle quality/myosteatosis	CT-derived skeletal muscle radiodensity (SMR) at the L3 vertebral level, in Hounsfield units (HUs).	Opportunistically during CT-based assessment at transplant evaluation; repeat when clinically appropriate	<33 HU in men and <28 HU in women. Other studies have used BMI-based thresholds [23]	Provides an objective measure of muscle quality that complements muscle quantity/sarcopenia; obtained from routinely available CT imaging without additional patient effort	Measurement and radiodensity thresholds vary across studies and methods, limiting universal standardization. 33/28-HU thresholds require external validation.	Nutritional optimization; exercise/prehabilitation; perioperative risk stratification and planning; longitudinal monitoring of muscle quality and clinical trajectory

8. Implications for Allocation Policy

The role of frailty in liver transplant allocation can be a very important factor. We know from published data that the prognostic signal is consistent across several cohorts. Frail patients have higher waitlist mortality than non-frail patients with similar MELD-based scores, but translating that knowledge into consistent allocation policy can prove difficult. Frailty measurement may not be standardized across centers participating in the same transplant allocation system. Even with validated tools like the Liver Frailty Index, technique and interpretation can vary. Frailty does not compete with current MELD-based allocation models but complements it. Frailty adds independent prognostic information when layered onto current MELD-based allocation models and larger cohorts have confirmed that functional status predicts outcomes even after accounting for MELD-based allocation.

At the level of prognostic assessment, frailty can refine individual risk estimation by capturing physiologic reserve and functional vulnerability that are not represented by MELD-based scores. The Liver Frailty Index and other validated frailty assessment tools could thus be useful to identify patients who should be monitored more closely, prehabilitation optimized, nutritionally rehabilitated and have their perioperative plans optimized. Frailty assessment is not a substitute for MELD-based scores, but is complimentary, as it helps to capture functional reserve and vulnerability.

Frailty assessment should also inform, but not independently determine, transplant candidacy and listing decisions. Clinicians can use frailty to refine risk valuation when current MELD-based allocation models may not match clinical assessment. Current evidence does not support using frailty as an exclusion criterion for liver transplantation. Instead, frailty should help clinicians determine the intensity and urgency of optimization and perioperative support for otherwise appropriate transplant candidates. While frailty has a consistent prognostic association and may be a marker of mortality risk that is not reflected in MELD-based scores, there is no universally standardized way to directly include frailty in allocation scores. Variability may exist across centers due to differences in assessment tools, testing technique, timing, and interpretation. The use of more functional measures may lead to subjective interpretation and may also be disadvantageous for patients with a reversible functional impairment or social and environmental factors. These considerations suggest that frailty should not be used as a direct criterion for allocation priority without a standardized measurement, proper validation and protection against inequitable use.

9. Conclusions

Frailty and sarcopenia provide complementary measures that capture important risks not fully reflected by MELD-based scoring systems. Routine assessment of functional status and muscle health may improve risk stratification, support timely prehabilitation and inform peri-transplant management. Importantly, frailty should be viewed as a dynamic and potentially modifiable risk state rather than an absolute contraindication to liver transplantation. Integrating serial frailty assessment with evaluation of muscle mass may provide a more comprehensive approach to the assessment and management of liver transplant candidates. The most useful current role of frailty assessment is adjunctive prognostic and clinical-management tool with improving individual risk assessment, guiding prehabilitation and flagging patients whose vulnerability MELD-derived scoring alone cannot see. Future allocation systems may include standardized measures of frailty or functional reserve, but such methods should be supported by prospective validation and equitable implementation.

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Abbreviations

The following abbreviations are used in this manuscript:

MELD-Na	Model for End-Stage Liver Disease with Sodium
MELD	Model for End-Stage Liver Disease
LFI	Liver Frailty Index
CFS	Clinical Frailty Scale
ICU	Intensive Care Unit
HR	Hazard Ratio
CT	Computed Tomography
BMI	Body Mass Index
HCC	Hepatocellular Carcinoma
MEDLINE	Medical Literature Analysis and Retrieval System

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