CHAPTER – 17

Frailty and Transplant Surgery

Background:

Frailty has been linked to a higher risk of negative postoperative outcomes in general surgery.[1] It has also been identified as a predictor of prolonged hospital stays and early readmission (EHR).[2, 3] Furthermore, independent of age, frailty has been identified as the strongest predictor of 30-day postoperative complications.[4] Frailty's impact on kidney transplant outcomes has been widely studied, but only infrequently. Furthermore, with a selection bias for those who have been authorized for transplantation, evaluating the risks of frailty on post-transplant outcomes may be difficult.[4] This chapter aims to elaborate on various solid organ transplantation and the involved risk in frail patients.

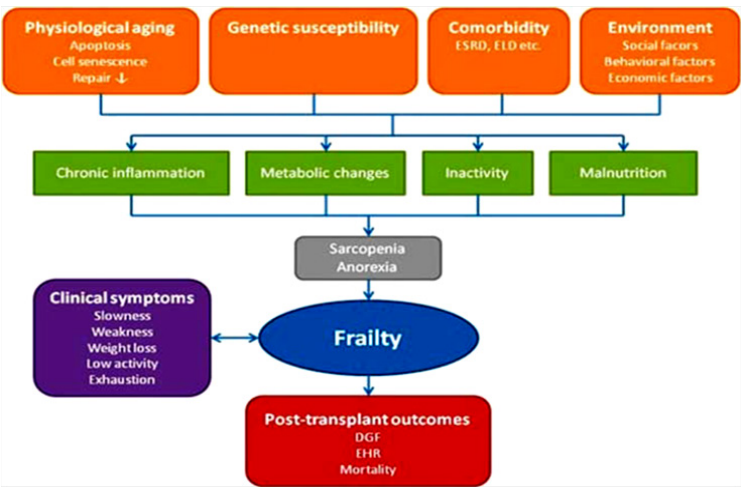


Figure 1: Risk factors, pathophysiological changes, clinical symptoms effects on post-transplant outcome. ELD indicates end-stage liver disease.[4]

Frailty considerations in kidney transplantation: Chowdhury et al found that the FFP was the most commonly used frailty assessment tool, accounting for 72% of the studies, despite significant heterogeneity in its interpretation, in a systematic review of studies on the association of frailty and chronic kidney disease (CKD) that included over 36 000 patients. [5] Frailty is related with CKD, and the incidence of frailty in CKD increases as renal function declines. Using the FFP, Fitzpatrick and colleagues discovered that 52% of dialysis patients were frail.[6] McAdamsDeMarco and colleagues conducted a cohort study and found that 18% of patients on the kidney transplant waiting list and 20% of kidney transplant recipients were frail through FFP.[7, 8]

Furthermore, McAdamsDeMarco and colleagues discovered that frailty at the time of kidney transplant evaluation was linked to a 2.8-fold increased risk of fair or poor health-related quality of life (HRQOL), a 2.9-fold increased risk of declining HRQOL while waiting for kidney transplantation, and a 2.2-fold increased risk of waitlist mortality in this large cohort.[7,9]Moreover, frail kidney transplant recipients have a 2.1-fold higher risk of delirium [10], a 1.6-fold higher risk of longer hospital stays [11], a 0.9-fold higher risk of delayed graft function[12], a 0.6-fold higher risk of early hospital readmission[13], a 0.3-fold higher risk of immunosuppression intolerance[14], and a 2.2-fold higher risk of death[15].

In patients with end-stage renal illness, low physical function assessments and difficulty to conduct activities of daily living (ADLs) have both been linked to a higher risk of mortality (ESRD).[16,17] The United Network for Organ Sharing (UNOS) registry data of 10,875 kidney transplant recipients was analysed using the Medical Outcomes Study Short Form 36 (SF36) Physical Component Scale (PCS) questionnaire to evaluate physical function. Low physical function was found to be an independent predictor of mortality (HR = 1.7).[18] Lower extremity impairment as measured by the SPPB, another objective marker of frailty, is linked to poor outcomes following kidney transplantation and a longer length of stay in the renal transplant hospital.[19] According to a recent study,

the prevalence of lower extremity disability was higher in the frail group of kidney transplant patients (70%) compared to the overall cohort of frail and non-frail kidney transplant recipients (47%). [20] Importantly, regardless of the frailty phenotype, impairment was linked to a 2.3-fold increased risk of death.

Small, randomized trials of individuals with CKD and ESRD have shown that rehabilitation regimens can help dialysis patients prevent or reverse sarcopenia and enhance physical performance. [21] Dependent hemodialysis patients may benefit from integrated inpatient rehabilitation to help them restore function.[22] The key points in kidney transplantation is elaborated in table 1.

Table 1: Key points in kidney transplantation[23]

1. Frailty is common in patients with CKD (pre-transplant and post-transplant) and ESRD with numerous negative implications for health status.
2. The ideal components of the frailty metric for kidney transplant candidates and recipients are unknown; studies to compare metrics, harmonize measurements, and identify an ESRD□specific measure of frailty would be of value.
3. Patients identified to be frail may benefit from physical therapy and rehabilitation, and additional studies are needed to understand how such interventions affect outcomes in kidney transplant candidates and recipients.

Frailty considerations in liver transplantation:

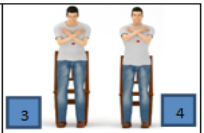
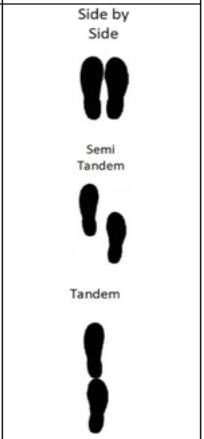
Frailty applications in liver transplantation have primarily focused on the physical dimension of the construct (example: FFP), but they have lately expanded to include assessments that capture functional capability and disability. Physical frailty is common in cirrhotic patients: the frequency of frailty in outpatients ranged from 17% to 35% according to

the FFP, and was assessed to be 38% by the SPPB; inpatients, 68% were functionally impaired according to the Karnofsky Performance Scale 70%. [24,25,26] Frailty has been found to be a significant predictor of liver transplant outcomes, including hospitalizations and mortality, both before and after the procedure.[27,28]

In this population, a variety of techniques for measuring frailty and physical function have been examined, and the Liver Frailty Index (LFI) is the result of recent efforts to standardise frailty testing in liver transplantation.[5,25] The LFI was developed expressly to capture the notion of physical frailty in liver transplant candidates and is a powerful predictor of waitlist mortality. It includes handgrip strength, chair stands, and balance testing. It classifies waitlist mortality more accurately than the MELDNa score alone. This metric is simple to use and score on a continuous scale, making it ideal for use in a liver transplant environment. To standardise the incorporation of frailty into center-level transplant decision-making, we recommend for the implementation of the LFI in baseline and longitudinal examinations of liver transplant patients.[23]

Table 2: Liver Frailty Index [5, 25]

Test	Instructions	Image
Gender	Male/Female should be noted	
Grip strength: The average of three trials, measured in the subject's dominant hand using a dynamometer	Allow the patient to grip the dynamometer in the standard position with their dominant hand (as shown below). The hand dynamometer is usually set to the second position while testing grip strength. Request that the patient squeeze the gadget as hard as they can and then release it three times. Keep track of the value in kilogrammes for each serial test. After each attempt, make sure to reset the device to zero. When grasping the device, do not allow the patient to rest it on any surface.	
Timed chair stands: This is measured as the number of seconds it takes to do five chair stands with the subject's arms folded across the	This is the amount of time it takes a patient to stand and sit in a chair five times without using their arms. The arms should be crossed over the chest. Start the timer when they first get up from their chair and stop it when they	

chest	reach their fifth chair rise. Enter 0 for the time if the patient cannot do all 5 chair stands in 60 seconds.	
Balance testing: It is measured as the number of seconds that the subject can balance in three positions (feet placed side-to side, semitandem, &tandem) for a maximum of 10 seconds each.	The patient is asked to perform three different postures for ten seconds each. Start the timer for each position when the patient's feet are in the proper position and they have let go of any support. Stop the timer, tell them that they must hold the entire 10 seconds for it to count, and ask if they want to try again if they catch themselves. Record the time in seconds to one decimal place if they don't finish the entire ten seconds. If they can hold a pose for 10 seconds, record that timeand move on to the next pose.	
With these three individual tests of frailty, the Liver Frailty Index must be calculated using the following equation: (−0.330×gender-adjusted grip strength)+(−2.529×number of chair stands per second)+(−0.040×balance time)+6 or a calculator can be used to calculate the same (calculator available at: http://liverfrailtyindex.ucsf.edu)		

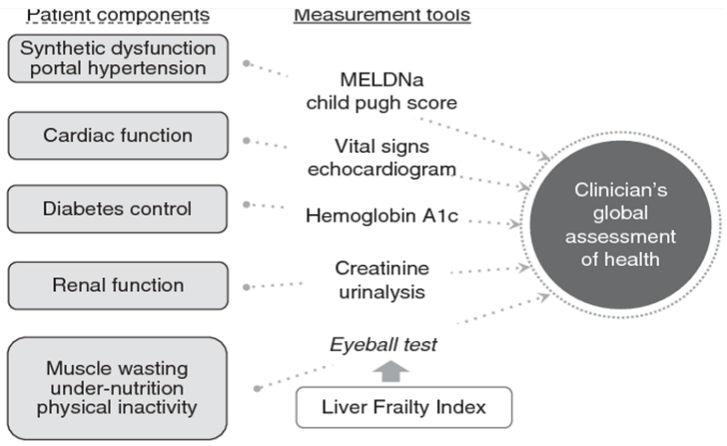


Figure 2: A conceptual model of some of the patient components that clinicians incorporate into their global assessment of a patient's health and the tools that they use to inform this holistic assessment.[27]

Image source: Lai JC, Covinsky KE, McCulloch CE, Feng S. The liver frailty index improves mortality prediction of the subjective clinician assessment in patients with cirrhosis. Am J Gastroenterol. 2018; 113(2): 235.

The pathophysiology of frailty in individuals with cirrhosis is multifactorial, and includes under-nutrition from poor oral intake, low physical activity, systemic inflammation, and hypogonadism. The contributions of hepatic synthesis dysfunction in increasing muscle protein degradation, as well as the negative effects of poor ammonia detoxification on muscle health, are unique to cirrhosis.[29] Each of these factors hastens the onset of sarcopenia, which is a key element in the pathophysiology of frailty. Sarcopenia affects anywhere from 22% to 70% of liver transplant candidates.[30]

Understanding the pathophysiology of cirrhosis-specific frailty has revealed a slew of potential intervention targets, and it's quickly becoming the next frontier in liver transplantation frailty research. Several short trials of exercise therapies, some of which included food counselling, have shown improvements in muscle mass, muscle strength, exercise capacity, HRQOL, and reductions in portal hypertension in individuals with cirrhosis.[31] In a single randomized clinical trial of intramuscular testosterone in hypogonadal males with cirrhosis, improvements in muscle mass were seen, with a trend toward strength gains.[32]

While there is currently minimal evidence on the topic of rehabilitation prior to liver transplantation, early studies are encouraging, leading to the conclusion that physical frailty, or at least some of its components, can be modified in liver transplant candidates. More research into establishing rehabilitation programmes that address frailty components with the objective of enhancing outcomes such as survival and HRQOL before and after liver transplantation should be

done.[23] Key points to be considered in liver transplantation are mentioned in Table 3.

Table 3: Key points in liver transplantation [23]

1. Frailty is prevalent and a critical determinant of poor outcomes.
2. Frailty measurements should be standardized and performed routinely in patients undergoing evaluation for liver transplantation.
3. Although subjective screening tools may be useful for quickly identifying patients vulnerable to poor outcomes, performance based tools better assess response to interventions and inform candidate selection.
4. Poor caloric intake, low physical activity, and muscle depletion are integral components of frailty and represent potential targets for intervention through rehabilitation programs.

Frailty considerations in lung transplantation:

Frailty may be linked to increased morbidity and death before and after lung transplantation, according to new research. Frailty's predictive value in lung transplantation has been studied in three trials so far. Singer et colleagues found that phenotypic frailty, as measured by the FFP or the SPPB, was common in lung transplant candidates and was linked to impairment, delisting, or death prior to surgery, as well as 1 and 4 year mortality following surgery.[33, 34] Wilson and colleagues found that using the frailty deficit measure, increasing cumulative deficits revealed a significant frequency of frailty (45% in 102 patients) and was independently related with shorter post-transplant survival.[35]

Frailty assessment before transplantation has the potential to improve risk categorization and candidate selection. It's crucial to remember that the right frailty index should appropriately assess risk for the desired goal. The FFP, for example, includes elements that are likely to improve after lung transplantation (such as slowness and weight loss), whereas the cumulative frailty deficits index may change less

or even worsen with the development of new extrapulmonary comorbidities (such as diabetes and renal dysfunction) even after a successful transplant.[36]The best frailty assessment, the usefulness of frailty instruments for candidate selection, and which frailty parameters are most receptive to rehabilitation pre and post lung transplantation are all open concerns.[37] Phenotypic frailty was reversible in a group of non-transplanted chronic obstructive pulmonary disease patients who completed pulmonary rehabilitation, suggesting that frail lung transplant candidates could improve significantly from rehabilitation.[38]

Several therapies to ameliorate frailty in lung transplant candidates were explored, with the acknowledgement that more research is needed to determine their effectiveness. These interventions included the following points:[23]

1. A consultation with a nutritionist and the possibility of nutritional supplementation
2. Enrolment in a physical therapy programme and/or an integrated pulmonary rehabilitation programme
3. Geriatric consultation to identify and improve factors that may be contributing to frailty, such as polypharmacy and cognitive impairment. Furthermore, assessment of social work services must be done in order to improve social support.

Key points that must be remembered during lung transplantation are enlisted in table 4.

Table 4: Key points in lung transplantation [23]

1. Phenotypic frailty is prevalent in lung transplant candidates.
2. Increased cumulative deficits are independently associated with lower post-transplant survival.
3. Candidate selection is fundamentally dependent on establishing the validity of frailty measures and demonstrating their strongand independent association with outcomes after lung transplantation.
4. Potential interventions to reverse frailty that require further study include pulmonary rehabilitation and

nutritional supplementation.

Frailty considerations in heart transplantation:

Frailty prevalence in advanced heart failure ranges from 25% to 78%, depending on the instrument and individual criteria used to define frailty. Heart failure and frailty have similar symptoms that can be attributed to either condition (For example: fatigue, exhaustion, weight loss).[39] Jha and colleagues found that one-third of their heart failure patients were frail, regardless of their age, gender, or ejection fraction.[40] Frail patients had a 54% one-year survival rate compared to 79%t for non-frail individuals. Furthermore, non-frail individuals who received a heart transplant had a 100% one-year post-transplant survival rate, compared to 52% in frail patients.[41] Sarcopenia of the pectoralis muscle on chest CT has been proven to be highly selective in its capacity to predict risk of mortality after mechanical circulatory support device (MCSD) therapy. Assessment of the efficacy of this muscle is another way to assess frailty. [23]

The rehabilitation of frail individuals prior to heart transplantation has piqued interest. The use of an MCSD in advanced heart failure patients reveals that about half of the patients improve their frailty level, but the remainder of patients remain prefrail. Certain cardiologists, in particular, did not believe that rehabilitation was a realistic therapeutic choice for patients since improvement in frailty would be small and patients would be at a higher risk of death.[23] Appropriate patients should be considered for MCSD therapy so that rehabilitation can continue. Normalization of cardiac output, restoration of end-organ balance, reversal of the catabolic condition of heart failure, improvement of muscle mass, and elimination of inactivity would all be possible with an MCSD.

A team of cardiologists highlighted the crucial need for more evidence to establish optimum frailty metrics in heart failure and to determine their potential predictive value compared to currently accepted methods.[23] Nonetheless, considering the large amount of data surrounding the FFP, it was decided that a modification of the FFP was the best tool to assess frailty in

clinical practise at this time, and that it should be included in future research studies. The inclusion of weight loss (due to predicted volume shifts) and the use of the Duke Activity Status Index (DASI) to measure activity are two changes to the standard FFP.

Because many patients with end-stage organ failure are hospitalized or critically ill during the transplant evaluation process, a comprehensive FFP is impractical, and handgrip strength alone should be used to diagnose frailty in these patients. Although depression and cognition are significant factors to examine, the enhanced predictive value of these domains must be confirmed before they can be recommended for inclusion in regular physical frailty tests.Key points in heart transplantation are mentioned in table 6.

Table 5: Key points in heart transplantation

1. When evaluating patients for heart transplantation or MCSD, a modified FFP should be used and is currently the most well□validated tool.
2. Frailty is at least partially reversible with durable MCSD through improved circulation, nutrition and structured rehabilitation programs.
3. A multi□center Frailty in Advanced Heart Disease Consortium should be developed to assess the relationship between the proposed frailty measures and outcomes. Patient□reported outcomes such as qualityof life after an intervention (eg, MCSD implantation or heart transplantation) are important and should be collected serially.

Prehabilitation and precautions to be taken ahead of any solid organ transplantation is enlisted in table 6.

Table 6: Possible Interventions for Optimizing Frail Transplant Candidates Interventions[23]

Organ	Possible interventions
Kidney	• Exercise • Physical therapy • Intergrated inpatient rehabilitation
Liver	• Center-based rehabilitation programs • BMI-stratified caloric intake targets (20 to 40 kcal/kg/day) • Targeted protein intake (1.2-1.5 g/kg/day) • Exercise
Lung	• Nutrition supplementation • Physical therapy • Pulmonary rehabilitation •Intervention by social workers/ psychologists
Heart	• Nutrition supplementation • Exercise • Physical rehabilitation • Mechanical circulatory support device

Summary:

A large increase in older transplant patients has occurred from improved health care and demographic changes. It's difficult to accurately assess the prevalence of frailty in people with end-stage organ failure. The characteristics of organ failure and the indications of frailty are very similar. The Minnesota Leisure Time Activity Scale, which is used to assess physical activity in the general population, is unable to make this distinction. Individuals with organ failure require a comprehensive tool that integrates objective and dynamic measurements of frailty and allows for the evaluation of prospective therapies prior to transplantation.

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