Frailty and the Selection of Patients for Destination Therapy
Left Ventricular Assist Device

Kelsey M. Flint, MD; Daniel D. Matlock, MD, MPH; JoAnn Lindenfeld, MD; Larry A. Allen, MD, MHS

Frailty is the aggregation of subclinical physiological insults across many organ systems resulting in a syndrome of heightened vulnerability in the face of stress. Measures of frailty are highly predictive of adverse outcomes in many medical and surgical populations but have never been formally applied to patient selection for destination therapy LVAD. Patients with severe heart failure being considered for destination therapy LVAD often have advanced age or noncardiac morbidity that renders them ineligible for transplantation. At the same time, these patients should have reasonable life expectancy to adequately realize the benefits of LVAD. As such, destination therapy LVAD-eligible patients are in a precariously narrow state of health often marked by a high degree of frailty. However, distinguishing frailty that will reverse with LVAD therapy (LVAD-responsive frailty) from frailty that will not (LVAD-independent frailty) is challenging. In this review, we summarize existing tools for destination therapy LVAD patient selection, define the syndrome of frailty, propose a conceptual distinction between LVAD-responsive frailty and LVAD-independent frailty, extrapolate the existing frailty literature to destination therapy LVAD-eligible patients, and identify directions for future research, including systematic collection of preoperative gait speed in this patient population.

Left ventricular assist devices (LVADs) for destination therapy (DT) are increasingly used in patients with advanced heart failure with reduced left ventricular ejection fraction who are ineligible for heart transplantation. The most common reason for heart transplant ineligibility is advanced age, although pulmonary hypertension, renal failure, recent cancer diagnosis, and diabetes mellitus with end-organ damage are also exclusion criteria. Therefore, DT LVAD candidates are older (mean age, 61.7 years for DT compared with 52.7 years for all other ventricular assist devices) and have significantly worse multimorbidity than other ventricular assist device candidates. Advanced heart failure itself leads to considerable morbidity, including exercise impairment, muscle wasting, and cognitive dysfunction. This combination of advanced age, comorbid disease, and heart failure-related morbidity often leads to the syndrome of frailty.

Frailty is defined as impairment in multiple, interrelated organ systems causing decreased homeostatic reserve and increased vulnerability to stress. Measures of frailty, even after adjustment for age and comorbidity, are highly predictive of death, incident disability, and hospitalization in patients with heart disease and those undergoing cardiac surgery. Application of objective measures of frailty to the related area of mechanical circulatory support is a logical extension of this novel prognostic domain. However, LVAD implantation presents a unique situation in which 1 of the major potential underlying causes of frailty—left ventricular dysfunction—can be reversed by the surgical procedure. This raises several important questions about the use of existing frailty measures applied to the LVAD setting. This article reviews the potential role of frailty in patient selection for DT LVAD.

Current Status of Patient Selection in DT LVAD
The mortality, morbidity, and costs of LVAD therapy are substantial. Although survival and cost-effectiveness continue to improve over time, calculated 2-year actuarial survival in the HeartMate II DT trial was only 58%, and the rate of disabling stroke was 11% per year. Additionally, 5-year cost is estimated at $360 000. Therefore, judicious application of DT LVAD to carefully selected patients is critical. Despite the importance of patient selection, the survival rate of patients undergoing placement of first-generation pulsatile LVADs was static over the decades; they were most commonly used. This suggests that improvements in DT LVAD outcomes have come primarily from advances in device technology and not from refinements in patient selection.

Although the Centers for Medicare and Medicaid Services have published strict criteria for DT LVAD eligibility and several risk assessment tools have been developed to predict postoperative complications and mortality (Table 1), choosing the optimal patient for DT LVAD remains a crudely defined art.

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286
Table 1. Existing Risk Models for Predicting Death or Adverse Outcome After LVAD Implantation

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Outcome(s) Predicted by the Risk Score</th>
<th>Patient Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>HeartMate II risk score(^{21})</td>
<td>Independent predictors of 90-d mortality: older age, lower albumin, higher creatinine, higher INR, implant before May 2007, and less center experience</td>
<td>Participants in the Thoratec HeartMate II BTT(^{22,23}) and DT(^{\text{t}}) trials; participants were randomly divided into derivation (n=583) and validation (n=539) cohorts</td>
</tr>
<tr>
<td></td>
<td>Independent predictors of 2-y mortality: older age and decreased implant center experience only</td>
<td>222 patients receiving HeartMate XVE device as DT</td>
</tr>
<tr>
<td>Destination therapy risk score(^{24})</td>
<td>90-d in-hospital mortality calculated from the following variables, each of which predicts worse mortality: platelets ≤148×10^3/μL, albumin ≤3.3 g/dL, INR &gt; 1.1, vasodilator therapy at time of implantation, mean PAP ≤25 mm Hg, AST &gt;45 U/L, hematocrit ≤34%, BUN &gt;51 U/dL, and no intravenous inotropes</td>
<td>104 patients (93% BTT, 7% DT) with the HeartMate Intraperitoneal (n=17), Thoratec LVAD (n=2), HeartMate XVE (n=51), HeartMate II (n=33) or Abandoned (n=1) device</td>
</tr>
<tr>
<td>Seattle Heart Failure Model (SHFM)(^{25})</td>
<td>Estimated 1-mo survival, as measured by the SHFM, is predictive of actual 1-y survival in a subset of patients with ambulatory LVADs 1-y mortality was 83% in the high-risk group (predicted 1-mo mortality &gt;20%), and 57% in the low-risk group (predicted 1-mo mortality ≤20%; P=0.04)</td>
<td>535 patients with 1 of the following devices: HeartMate IP1000, Vp, XVE and II, Micromed-Debakey, Novacor, Thoratec percutaneous VADs and intravascular VADs</td>
</tr>
<tr>
<td>Model for End Stage Liver Disease (MELD)(^{26})</td>
<td>Operative mortality (intraoperative or ≤30-d postoperative mortality): 60% increase in mortality for every 5-unit increase in MELD score 6-mo mortality: patients with a preoperative MELD ≥17 had 15% increase in 6-mo mortality compared with patients whose MELD was &lt;17 Total blood product use during surgery: for every 5-unit increase in preoperative MELD score, total blood product requirement increased by 20 ±4.0 units (R(=0.011), P&lt;0.001)</td>
<td>484 patients enrolled in the HeartMate II BTT trial(^{22,23})</td>
</tr>
<tr>
<td>Right ventricular failure risk model(^{27})</td>
<td>Independent predictors of right ventricular failure following LVAD implantation: CVP/PAP ratio &gt;0.63, preoperative ventilatory support, and BUN &gt;39 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

LVAD indicates left ventricular assist device; INR, international normalized ratio; PAP, pulmonary artery pressure; AST, aspartate transaminase; BUN, blood urea nitrogen; CVP, central venous pressure; DT, destination therapy; VAD, ventricular assist device; BTT, bridge to transplantation.

Appropriate DT LVAD candidates fall into a precariously narrow state of health, having sufficiently advanced heart disease to warrant device placement (Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Level 2–3) at the same time as also being stable enough to survive the operation (avoid INTERMACS Level 1).\(^1\) In addition, DT LVAD-eligible patients must be without significant noncardiac morbidity that would prevent meaningful postoperative improvement.\(^28\) Finally, LVAD therapy involves meticulous care of the percutaneous driveline site, system operation, anticoagulation, and frequent encounters with the healthcare system.\(^{28,29}\) All of these issues are more challenging in the presence of frailty and highlight the need for more comprehensive measures of risk when attempting to select patients who will benefit from LVAD therapy.

Definitions of Frailty

To understand how frailty may relate to DT LVAD, it must first be broadly defined. The concept of frailty lacks a widely accepted definition despite being a well-recognized entity among clinicians.\(^5,30\) At its core, frailty is the aggregation of subclinical physiological insults across many organ systems resulting in a syndrome of heightened vulnerability in the face of stress.\(^4\) The so-called “eyeball test,”\(^16,31\) an overall assessment of the patient from the doorway, is often used by clinicians to intuitively qualify this vulnerability. Because frailty lacks a unifying definition,\(^32\) measures are varied, ranging from purely physical function\(^{33,34}\) to more extensive evaluations encompassing disability, comorbidity, and social vulnerability\(^5,35\) (Table 2; online-only Data Supplement Table).

Although frailty is associated with advanced age, it is not confined to older populations nor does advanced age equate to frailty. Measures of frailty inherently work to distinguish highly vulnerable patients from those who are not, even among older adults.\(^32\) Older age is associated with a poorer prognosis in widely used LVAD risk models derived from randomized controlled trials and a number of single-center experiences (Table 1), yet not all series have shown age to necessarily predict worse outcomes. In 1 center, LVAD recipients ≥70 years old (range, 70–87 years) had similar short- and long-term survival compared with those <70 years old (range, 16–69 years).\(^48\) This suggests that carefully selected older adults can be appropriate for DT LVAD,\(^49\) perhaps because frailty, rather than chronological age, is the more important driver of risk for adverse outcomes in older adults. As such, the current absence of an absolute upper age cutoff for DT LVAD eligibility may be appropriate, but only with careful consideration of other factors known to be increasingly prevalent with advanced age.

Prognostic Value of Frailty in Non-LVAD Populations

Despite some variation in what is considered frailty, nearly every proposed definition has proven to predict adverse outcomes.\(^3\) As such, frailty is an important component of...
clinical decision-making processes, particularly regarding older adults. Frailty measures have been applied to several populations that are reflective of DT LVAD candidates. Studies of older adults with heart failure, significant coronary artery disease, acute coronary syndromes, and percutaneous coronary intervention have shown that frailty is predictive of short- and long-term mortality, myocardial infarction, incident disability, hospitalization or rehospitalization, and length of hospital stay.

For example, in a study of nearly 35,000 community-dwelling adults aged >65 years, short-distance gait speed, a common frailty measure, predicted 10-year survival ranging from 19% to 87% in men and 35% to 91% in women. Slower gait speed accurately predicted mortality, even when compared with the combination of chronic conditions, smoking history, body mass index, and hospitalization. In surgical patients, baseline frailty predicts postoperative morbidity and mortality, and prolonged length of hospital stay. In 1 study of older patients undergoing cardiac surgery, slow gait speed, even after adjustment for the Society of Thoracic Surgeons risk score, had an OR for in-hospital postoperative morbidity or major morbidity of 3.05 (95% CI, 1.23–7.54).

Application of Frailty to DT LVAD Candidates

Although extending measures of frailty from heart failure and surgical populations to the related area of mechanical circulatory support would seem logical, LVAD implantation has the unique capacity of reversing cardiac contributions to frailty. Therefore, we propose 2 hypothetical etiologies of frailty relevant to the DT LVAD population: "LVAD-responsive frailty" (ie, resulting directly from heart failure) and "LVAD-independent frailty" (ie, resulting from nonheart failure-related illness; Figure A). An effective frailty measure would not only quantify the degree of frailty, but also help distinguish LVAD-responsive frailty from LVAD-independent frailty, thus enhancing clinicians' ability to identify patients most likely to experience significant benefit from DT LVAD (Figure B). To date, frailty research has only begun to explore this concept in the postoperative setting.

Prior studies show that measures of frailty can improve in some older adults and that this improvement is associated with better outcomes. For example, Hardy et al reported that among community-dwelling older adults, persistent improvement in gait speed led to significantly lower mortality compared with those whose gait speed never improved. However, specific measures that can help identify reversible from irreversible frailty are unknown.

Furthermore, existing frailty measures tend to use variables influenced by both heart failure and nonheart failure morbidity. For example, nutrition, physical performance, and cognition can all be adversely affected by cardiac and noncardiac organ dysfunction. Therefore, measures that could help distinguish LVAD-responsive from LVAD-independent frailty may do so either by identifying physiological parameters specific to heart failure-related frailty or conversely by quantifying the degree of general frailty out of proportion to more traditional measures of heart failure severity (Figure B).

Finding a Frailty Measure for DT LVAD Selection

The wide range of existing frailty measures (Table 2; online-only Data Supplement Table) sets the groundwork for characterizing frailty in DT LVAD-eligible patients. The Fried criteria and Short Physical Performance Battery are highly predictive of adverse outcomes in a variety of settings and therefore have garnered attention in the frailty literature. Multidimensional frailty measures such as the Rockwood Index address multiple domains, including disability (eg, impairment in activities of daily living), multiple comorbidity, nutrition status, cognitive function, and physical performance. However, multidimensional frailty measures vary widely in composition from 1 measure to another, are inherently more cumbersome, and may be difficult to apply in certain clinical settings.

Fortunately, single items from composite measures also appear to successfully characterize general frailty and may be more practical in the DT LVAD population. Several studies have examined short-distance gait speed at usual pace as a single frailty measure. For example, in a report of 309 patients with significant coronary artery disease, gait speed alone was the most accurate predictor of 6-month mortality when compared with the Fried criteria and Rockwood Index. Another study reported that the Fried criteria predicted postprocedure mortality in patients ≥65 years old undergoing percutaneous coronary intervention. However, in the associated editorial, Chaudhry et al advocated for gait speed alone as the ideal frailty measure because it is time- and resource-efficient at the same time as still providing prognostic information not captured by traditional risk assessment (Table 2).

Another single component of the Fried criteria that confers significant predictive information is handgrip strength. In a study of >6000 men, midlife handgrip strength was independently predictive of 30-year mortality as well as incident disability and functional decline over 25 years. Handgrip strength is also correlated with operative risk in patients undergoing elective surgery.

Future Directions

Whether such objective measures of frailty can add significant incremental prognostic information in patient selection for DT LVAD remains to be determined. The validation of a parsimonious measure of frailty that has good predictive performance in the LVAD population is an important next step. Currently short-distance gait speed, as a proxy for frailty, is the leading candidate for such a measure. Gait speed has already been studied extensively in various populations (Table 2; online-only Data Supplement Table) and, for ambulatory patients, is easily incorporated into pre-existing DT LVAD research protocols and clinical settings. However, there is a significant minority of nonambulatory patients considered for DT LVAD (eg, intra-aortic balloon pump-dependent) for whom gait speed assessment is not possible. Alternative measures such as handgrip strength, which is less studied but feasible in the subset of patients who are unable to walk but still able to use their hands and follow commands, also deserves attention.
None of these proposed measures are designed to directly distinguish LVAD-responsive from LVAD-independent frailty. The current informal approach is to determine whether overall frailty is out of proportion to heart failure severity (eg, clinician’s eyeball test looks much worse than peak oxygen consumption). Perhaps incorporating more objective measures of general frailty (ie, gait speed) into this crude existing process will improve patient selection, but only systematic

Figure. A. Breakdown of frailty into its underlying causes, manifestations, and clinical outcomes separated by LVAD-responsive and LVAD-independent causes of frailty. Frailty is a heightened state of vulnerability in the face of stress and results from the accumulation of multimorbidity, aging, and disability. In advanced heart failure with reduced left ventricular ejection fraction, a patient’s heart failure contributes significantly to the frailty syndrome and is potentially reversible with LVAD (LVAD-responsive frailty). However, many patients with advanced heart failure may be frail due to illness unrelated to heart failure severity, which is not treatable with LVAD (LVAD-independent frailty). Heart failure-related and nonheart failure-related factors combine to adversely affect health outcomes through several common effectors of frailty. LVAD indicates left ventricular assist device; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; COPD, chronic obstructive pulmonary disease; LOS, length of stay; ICU, intensive care unit; ADLs, activities of daily living. B. Patients undergoing DT LVAD with similar total baseline frailty but differing underlying causes of frailty. Patient A, with primarily LVAD-responsive frailty (ie, mostly heart failure-related illness), is likely to experience a good outcome if he or she survives the early postoperative period. Conversely, Patient C, with primarily LVAD-independent frailty (ie, mostly noncardiac-related illness), is at greater risk of death, complications (eg, stroke, gastrointestinal bleed, or chronic hemolytic anemia) and/or persistently poor functional status after LVAD placement. Of note, most DT patients are more like Patient B with evidence of significant LV dysfunction warranting LVAD but also significant comorbidity and/or advanced age disqualifying them from transplantation. DT indicates destination therapy; LVAD, left ventricular assist device.
<table>
<thead>
<tr>
<th>Frailty Measure</th>
<th>Criteria</th>
<th>Population Studied</th>
<th>Outcomes Predicted by the Frailty Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fried criteria[^33]</td>
<td>1. Unintentional weight loss</td>
<td>Patients ≥65 y old undergoing outpatient elective surgery[^36]</td>
<td>30-d postoperative complications Discharge to a facility Increased length of stay</td>
</tr>
<tr>
<td></td>
<td>2. Weak handgrip strength</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>3. Self-reported exhaustion</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>4. Slow gait speed</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>5. Low self-reported physical activity</td>
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<td></td>
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<tr>
<td>Short Physical Performance Battery (SPPB)[^34]</td>
<td>1. Gait speed at usual pace over 8 feet or 4 meters</td>
<td>Patients ≥65 y old hospitalized for preexisting decompensated heart failure[^8]</td>
<td>Longer hospital length of stay 1-y mortality Rehospitalization Incident disability</td>
</tr>
<tr>
<td></td>
<td>2. Time taken to stand from a chair 5 times without using arms</td>
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<tr>
<td></td>
<td>3. Ability to stand with feet together, in tandem and semitandem positions for up to 10 s in each position</td>
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</tr>
<tr>
<td>Gait speed</td>
<td>Component of both the Fried criteria and SPPB</td>
<td>Patients ≥70 y old undergoing elective cardiac surgery[^14]</td>
<td>Death Major postoperative complication 6-mo mortality</td>
</tr>
<tr>
<td>Handgrip strength (HGS)</td>
<td>Measured using a hand dynamometer</td>
<td>Patients undergoing elective, non-cardiac surgery[^38–40]</td>
<td>Postoperative complications (eg, infection, renal failure, wound dehiscence, death)</td>
</tr>
<tr>
<td></td>
<td>Studies vary on whether the dominant or nondominant hand is used, no. of attempts, and correction for factors such as gender and height</td>
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<tr>
<td>Lee et al[^15]</td>
<td>Frailty defined as</td>
<td>Cardiac surgery patients</td>
<td>In-hospital mortality Prolonged institutional care Midterm mortality</td>
</tr>
<tr>
<td></td>
<td>1. Any one deficit in Katz index for ADLs[^41] and/or</td>
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<tr>
<td></td>
<td>2. Presence of dementia, and/or</td>
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<tr>
<td></td>
<td>3. Inability to ambulate independently</td>
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<tr>
<td>Frailty Index-Comprehensive Geriatric Assessment (FI-CGA)[^42]</td>
<td>Each of the following domains is assessed and scored to form the FI-CGA score</td>
<td>Patients ≥70 y old with significant coronary artery disease[^7]</td>
<td>Not predictive of 6-mo mortality in fully adjusted models</td>
</tr>
<tr>
<td></td>
<td>1. Cognitive status</td>
<td></td>
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<td></td>
<td>2. Mood and motivation</td>
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<td></td>
<td>3. Communication (vision, hearing, and speech)</td>
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<td></td>
<td>4. Mobility</td>
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<td></td>
<td>5. Balance</td>
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<tr>
<td></td>
<td>6. Bowel function</td>
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<td>7. Bladder function</td>
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<td></td>
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<tr>
<td></td>
<td>8. ADLs and IADLs</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>9. Need for help from nutrition or social resources</td>
<td></td>
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<tr>
<td></td>
<td>10. No. of comorbidities</td>
<td></td>
<td></td>
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<tr>
<td>Comprehensive assessment of frailty (CAF)</td>
<td>Each of the following domains is assessed and scored to form the CAF score</td>
<td>Adults ≥74 y old undergoing elective cardiac surgery[^16]</td>
<td>30-d mortality</td>
</tr>
<tr>
<td></td>
<td>1. Weakness</td>
<td></td>
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<td></td>
<td>2. Slow gait speed</td>
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<td>3. Self-reported exhaustion</td>
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<tr>
<td></td>
<td>4. Low physical activity</td>
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<td></td>
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<tr>
<td></td>
<td>5. Poor standing balance</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>6. Low serum albumin</td>
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<td></td>
<td>7. High brain natriuretic peptide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8. Low forced expiratory volume in 1 s</td>
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</tbody>
</table>

(Continued)
collection and statistical evaluation will answer that question. The ideal frailty measures in DT LVAD would be novel markers (eg, patterns of sarcopenia, hormone levels, or biomarkers of immune function) that could specifically measure noncardiac frailty, but currently no such measure exists. It remains to be seen whether any markers of frailty will add significant incremental prediction to current standards for pre-LVAD testing. Astute clinicians already attempt to weigh measures of cardiac dysfunction (eg, invasive hemodynamics, cardiac imaging, natriuretic peptides, peak oxygen consumption, etc) against measures of additional disease burden (eg, irreversible kidney disease, liver dysfunction, malnutri-
tus, and patient satisfaction are of vital importance to patients and payers. Frailty measures such as gait speed may be particularly useful in predicting many of these nonmortality end points. Additionally, the distinction between short- and long-term outcome prediction should receive careful attention. LVAD-responsive frailty will likely convey some transient degree of acute surgical risk; LVAD-independent frailty should manifest as a persistent risk for a wide variety of adverse outcomes.

Conclusions

At the same time that serial improvements in LVAD technology have led to the growing use of DT LVAD in certain transplant-ineligible patients with advanced heart failure, lack of significant improvement in the patient selection process hinders the optimal application of this therapy to those who are most likely to benefit from it. As a global summary of numerous multisystem physiological insults leading to vulnerability in the face stress, frailty may be an important additional predictor of patient-centered outcomes postimplantation. However, distinguishing LVAD-responsive frailty from LVAD-independent frailty is an essential consideration in the application of frailty measures to this setting. The simplicity and predictive value of short-distance gait speed in a number of similar patient populations make its systematic collection and validation a priority for future research in the rapidly growing field of DT LVAD.

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References


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### Supplemental Material

#### Studies of frailty by type of frailty measure

<table>
<thead>
<tr>
<th>Frailty Measure</th>
<th>Criteria</th>
<th>Scoring System</th>
<th>Population studied</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gait Speed</strong></td>
<td></td>
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</tr>
<tr>
<td>Afilalo, et al(^1)</td>
<td>Time to walk 5 meters at usual speed</td>
<td>Gait speed classified as either slow (≥ 6 seconds to walk 5 meters) or normal (&lt; 6 seconds to walk 5 meters)</td>
<td>131 patients undergoing CABG, valve replacement or both</td>
<td>Slow gait speed was an independent predictor of mortality or major morbidity following cardiac surgery (OR 3.17, 95% CI 1.17-8.59).</td>
</tr>
<tr>
<td>Purser et al(^2)</td>
<td>Gait speed was measured as part of the Fried criteria as time to walk 15 feet at usual pace.</td>
<td>Slow gait speed defined as ≤ 0.65 m/s.</td>
<td>309 consecutive patients ≥ 70 years old admitted to a cardiology inpatient service with at least 2 vessel coronary disease diagnosed by angiography.</td>
<td>- Compared to the Fried criteria and Rockwood Index,(^3) gait speed alone was the most robust predictor of 6-month mortality (OR 4.0, 95% CI 1.1 – 13.8 in fully adjusted model).</td>
</tr>
<tr>
<td>Studenksi et al(^4)</td>
<td>Gait speed measured in m/s over a range of distances (8ft – 6 m)</td>
<td>Gait speed was used as a continuous variable.</td>
<td>Individual participant data was pooled from 9 cohort studies of community</td>
<td>The age adjusted HR for death for every 0.1 m/s increase in gait speed was 0.88 (95% CI 0.87-0.90);</td>
</tr>
<tr>
<td>Hardy et al\textsuperscript{5}</td>
<td>Gait speed at usual pace over 4 meters</td>
<td>The \textit{a priori} \text{definition of “clinically significant change” in gait speed was 0.1 m/s over 12 months.}</td>
<td>487 community-dwelling patients (\geq 65) years old from 2 primary care clinics (a Veterans Affairs clinic and Medicare HMO clinic)</td>
<td>8-year mortality was significantly improved in patients whose gait speed improved by at least 0.1 m/s in the first 12 months versus those whose gait speed did not improve (HR 0.42 (95% CI 0.29 – 0.61)).</td>
</tr>
</tbody>
</table>
| Rantanen et al\textsuperscript{6} | HGS was measured with a hand dynamometer, and the average of two baseline values was used. | Divided HGS into tertiles: weakest tertile: < 37 kg; middle tertile: 37 – 42 kg; strongest tertile: > 42 kg | 3218 initially healthy men ages 45-68 who were followed for 25 years as part of the Honolulu Heart Program | In unadjusted and adjusted models, low HGS at baseline predicted incident disability during the 25-year follow-up. - Participants in the lowest and middle tertiles of HGS were more likely to walk slowly (\(\leq 0.4\) m/s) and less likely to be able to rise from a chair during the 25-year follow-up.
Rantanen et al.\textsuperscript{7} HGS was measured using a hand dynamometer and the best of three trials was used. HGS was measured using a hand dynamometer and the best of three trials was used. Participants were stratified by HGS tertile (weakest < 37 kg, middle 37-42 kg, strongest > 42 kg) and BMI (smallest < 20 kg/m\textsuperscript{2}, middle 20-24.99 kg/m\textsuperscript{2}, largest > 25 kg/m\textsuperscript{2}). Participants were stratified by HGS tertile (weakest < 37 kg, middle 37-42 kg, strongest > 42 kg) and BMI (smallest < 20 kg/m\textsuperscript{2}, middle 20-24.99 kg/m\textsuperscript{2}, largest > 25 kg/m\textsuperscript{2}).

- In fully adjusted models, RR of mortality over 30 years was 1.24 (95% CI 1.11 – 1.39) in the lowest vs. highest tertile of HGS and 1.14 (95% CI 1.03 – 1.26) for middle vs. highest tertile of HGS.

- In the lowest and middle tertiles of HGS, participants with BMI < 20 or ≥ 25 had greater mortality than those with BMI 20-24.99. However this relation was insignificant in the highest HGS tertile.

Giampoli et al.\textsuperscript{8} HGS was measured using a hand. HGS was analyzed by quartile (20-68). Incidence of disability increased as
HGS was measured using "a simple hand-grip dynamometer." Normal HGS values were obtained from 284 health volunteers undergoing minor operations. Weak HGS was defined as < 85% the mean HGS of controls.

Klidjian et al<sup>9</sup> HGS was measured with a hand dynamometer, taken as the best of 3 tries in the non-dominant hand. Normal HGS values were obtained from 203 healthy volunteers undergoing teeth extraction or other minor procedures. Weak HGS was defined as < 85% the mean HGS of controls.

Guo et al<sup>10</sup> HGS was measured with a hand dynamometer in the dominant hand. The higher of 2 attempts was used. Normal HGS values were obtained from 284 health volunteers undergoing major elective abdominal surgery. Weak HGS was defined as < 85% the mean HGS of controls.

Normal HGS values were obtained from 284 health volunteers undergoing minor operations. Weak HGS was defined as < 85% the mean HGS of controls. Normal HGS values were obtained from 203 healthy volunteers undergoing teeth extraction or other minor procedures. Weak HGS was defined as < 85% the mean HGS of controls.

Patients with HGS < 85% normal suffered significantly more major and minor complications than those with HGS ≥ 85% normal (p<0.004), and had longer length of hospital stay.
HGS was measured in the non-dominant hand. Predicted HGS values adjusted for age and sex were derived from HGS values from 247 healthy volunteers ages 16-97 years. Weak HGS was defined as < 85% predicted.

**Fried Criteria**

1. **Shrinking:**
   - Unintentional weight loss of ≥ 10 lbs in the past year or > 5% of body weight from the previous year.
   - 0 criteria met: robust or not frail
   - 1-2 criteria met: intermediate frail or prefrail
   - ≥ 3 criteria met: frail

   5,317 men and women ≥ 65 years old recruited for the Cardiovascular Health Study (CHS)

   - Frail participants had greater 3- and 7-year mortality, greater rate of first hospitalization, fall, and worsening ADL and mobility disability compared to intermediate-frail and nonfrail individuals (P<0.0001 for all outcomes).

2. **Weakness:** HGS in lowest 20% of the population at baseline, adjusted for gender and BMI.

3. **Exhaustion:** Self-reported

Webb et al. HGS was measured in the non-dominant hand. Predicted HGS values adjusted for age and sex had 74% sensitivity for predicting surgical complications. Grip strength < 85% predicted based on age and sex was 0.002.
exhaustion based on responses from 2 items on the CES-D questionnaire. 

4. Slowness: Gait speed in the slowest 20% at baseline, measured at usual pace over 15 feet and adjusted for gender and height.

5. Low activity:
   Self-reported physical activity in the lowest 20% at baseline.

Bandeen-Roche et al\textsuperscript{14} measured in Fried et al\textsuperscript{12} except that shrinking was defined as unintentional weight loss of ≥10% of weight at age 60 or BMI < 18.5 kg/m\textsuperscript{2}, 0 criteria met: robust or not for the Fried criteria\textsuperscript{12} in 1002 criteria\textsuperscript{12} in 1002 were comparable in the WHAS and CHS cohorts (frailty)

- The prevalence of frailty, intermediate frailty and non-frailty

- The prevalence of frailty, intermediate frailty and non-frailty

- The prevalence of frailty, intermediate frailty and non-frailty

- The prevalence of frailty, intermediate frailty and non-frailty
and gait speed was measured over 4 meters.

Women's Health and Aging Study (WHAS) I, and 436 less disabled, community-dwelling women ages 70-79 (WHAS II).

Makary et al. measured Fried criteria as measured in Fried et al. except that shrinking was defined only as unintentional weight loss of ≥ 10 lbs in the past year and HGS and gait speed were taken as the average of three trials. 594 patient ≥ 65 years old who presented to a university hospital clinic for elective surgery were included. Intermediate frailty and frailty predicted post-operative complications compared to not frail patients (OR 2.06, 95% CI 1.18-3.60 and OR 2.54, 95% CI 1.12 – 5.77, respectively).

- Intermediate frailty and frailty predicted post-operative complications compared to not frail patients (OR 2.06, 95% CI 1.18-3.60 and OR 2.54, 95% CI 1.12 – 5.77, respectively).

- Intermediately frail and frail patients had longer length of hospital stay compared to non-frail patients (incidence...
rate ratio 1.49, 95% CI 1.24 – 1.80 and incidence ratio 1.69, 95% CI 1.28 – 2.23, respectively).

- Frailty improved the predictive power of commonly used surgical risk scores (American Society of Anesthesiologists, the Lee score and the Eagle score, P<0.01)

<table>
<thead>
<tr>
<th>Singh et al&lt;sup&gt;19&lt;/sup&gt;</th>
<th>Fried criteria as measured in Fried et al&lt;sup&gt;12&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 criteria met:</td>
<td>Prospective cohort study of 629 patients who underwent percutaneous coronary intervention and survived to discharge. Fried criteria were measured at hospital admission and outcomes were not frail</td>
</tr>
<tr>
<td>1-2 criteria met:</td>
<td>629 patients who underwent coronary intervention and were intermediate frail</td>
</tr>
<tr>
<td>≥ 3 criteria met:</td>
<td>coronary frail</td>
</tr>
</tbody>
</table>

- Frailty predicted death (HR 5.36, 95% CI 2.41-11.9) and death and MI (HR 3.04, 95% CI 1.80 – 5.15) at 2 years in unadjusted analyses.

- Frailty added incremental prognostic value to the Mayo Clinic Risk Score in the prediction of death and MI (AUC
Boxer et al\textsuperscript{20} Fried criteria as described in Fried et al\textsuperscript{12}, except for gait speed, which was measured over 8 feet. Each criterion met counted as one point. These points were summed to make the frailty phenotype score. Boxer et al\textsuperscript{20} Fried criteria as described in Fried et al\textsuperscript{12}, except for gait speed, which was measured over 8 feet. Each criterion met counted as one point. These points were summed to make the frailty phenotype score.

59 patients with EF $\leq 40\%$ had the Fried criteria measured at baseline. Fried criteria were reassessed 4 years later in 19 participants. 20 patients did not participate, and 20 had died by the 4-year follow-up.

- In univariate analysis, higher frailty phenotype score significantly predicted death (HR 1.64, 95% CI 1.19 – 2.29).
- In multiple backwards Cox linear regression modeling, a one-point increase in the frailty phenotype score resulted in a 50% increase in mortality.

Rothman et al\textsuperscript{21} Fried criteria were measured as in Fried et al\textsuperscript{12} except for gait speed, which was measured as the time taken to walk quickly both directions over a 10 foot course. Each Fried criterion was treated as a separate, independent variable. 754 community-dwelling, non-disabled adults $\geq 70$ years old followed over a 72 month period. Slow gait speed was the strongest predictor of:

1) Chronic disability (HR 2.97, 95% CI 2.32 – 3.80)
2) Long-term nursing home stay (HR 3.86, 95% CI 2.37 – 6.23)
95% CI 2.23–6.67) 
3) Injurious falls (HR 2.19, 95% CI 1.33 – 3.60)

**Short Physical Performance Battery (SPPB)**

| Guralnik et al.22 | 1. Gait speed at usual pace over 8 feet or 4 meters | • Each criterion is scored from 0-4 non-disabled individuals and 1,946 initially non-disabled Hispanic individuals |
|                  | 2. Time taken to stand from a chair 5 times without using arms | • Sum of all 3 criteria is the summary performance score |
|                  | 3. Ability to stand with feet together, in tandem and semi-tandem positions for up to 10 seconds in each position | • Lower scores reflect greater frailty |
|                  | 4,588 initially non-disabled individuals and 1,946 initially non-disabled Hispanic individuals |

- Compared to those with summary performance scores of 10-12, those with summary performance scores of 4-6 had RR of 2.9-4.9 for developing mobility-related disability, depending on site and time of follow-up.
- Similarly, those with summary performance scores of 7-9 had a RR for developing disability was 1.5-2.1.

**Chiarantini et al.23**

- SPPB was assessed as described in Guralnik et al.22 Gait speed measured over 4 meters was assessed in quartiles of summary performance scores: 0, 1-4, 5-8 and 9-12.
- The study population was analyzed in All patients ≥ 65 years old admitted to two teaching hospitals in Italy with 4,588 initially non-disabled individuals and 1,946 initially non-disabled Hispanic individuals followed for 1-6 years for development of disability.
- Compared to participants with summary performance scores of 9-12, mortality was
as a separate variable. Patients with decompensated, pre-existing heart failure were followed for a median of 1.2 years. Patients scoring 0 (HR 6.06; 95% CI 2.19 – 16.76) and 1-4 (HR 4.78; 95% CI 1.63 – 14.02).

| Rolland et al<sup>24</sup> | 1. SPPB as described in Guralnik et al,<sup>12</sup> except that gait speed was taken as the fastest of 2 trials over 6 meters at usual pace. Summary performance score was divided into tertiles: 0-6 poor performance, 7-9 fair ≥ 75 years old, followed for a mean of 3.8 years. Observational study of 7,250 community-dwelling women, significantly predicting increased mortality included In fully adjusted models, variables slower gait speed trend), lower total summary performance score (p=0.02) and weaker HGS (p=0.01).
| Volpato et al<sup>25</sup> | 2. HGS was measured with a hand dynamometer in the dominant hand. The best of three trials was used (N/m²). SPPB as described in Guralnik et al<sup>22</sup> with gait speed measured over 4 meters. Summary performance score was analyzed by tertile (0-4, 5-7, 8-years old who patients ≥ 65 years old) in a fully adjusted multiple linear regression model, - In a fully adjusted multiple linear regression model, patients whose...
were hospitalized for either CHF, COPD, pneumonia or minor stroke. SPPB was evaluated on admission and upon discharge. Summary performance score was 8-12 had significantly shorter length of stay than those whose score was 0-4 (difference of 2.5 hospital days, p<0.036).

- A one-point increase in admission summary performance score correlated with a 0.5-day decrease in hospital stay (p<0.007).

Volpato et al\textsuperscript{26} SPPB as described in Guralnik et al,\textsuperscript{22} with gait speed measured over 4 meters. Summary performance score was analyzed by tertile (0-4, 5-7, 8-12) and as a continuous variable. 1-year observational study of 92 patients ≥ 65 years old hospitalized with a primary diagnosis of CHF, COPD, pneumonia or minor stroke. Compared to those with summary performance scores of 8-12, those with scores of 0-4 had an OR for mortality or hospitalization over 1 year of 5.38 (95% CI 1.82 – 15.9). Similarly those with scores of 5-7 had an
OR of 2.63 (95% CI 1.16 - 6.01).

- A one-point increase in summary performance score from admission to discharge was associated with a 14% decrease in risk of death or re-hospitalization over 1 year (95% CI 2-25% reduction).

Studenski et al. SPPB was measured as described in Guralnik, et al. As a separate variable, gait speed at usual pace was also measured over 4 meters with a 1-meter head start.

Summary performance score was divided into tertiles (< 7, 7-9.5, 10-12) and also analyzed as a continuous variable in 2-point increments. Gait speed was divided into low (<0.6 m/s), medium (0.6-1.0 m/s) and high (1.0 m/s) groups, and also treated as a community dwelling adults ≥ 65 years old recruited from a Veterans Affairs clinic and Medicare HMO clinic followed over 12 months for the outcomes of hospitalization, nursing home placement, death, and decline in functional status. Gait speed was divided into low (<0.6 m/s), medium (0.6-1.0 m/s) and high (1.0 m/s) groups, and also treated as a continuous variable in 2-point increments. Gait speed was divided into low (<0.6 m/s), medium (0.6-1.0 m/s) and high (1.0 m/s) groups, and also treated as a continuous variable in 2-point increments. Gait speed was divided into low (<0.6 m/s), medium (0.6-1.0 m/s) and high (1.0 m/s) groups, and also treated as a continuous variable in 2-point increments.

- Slow gait speed predicted greater risk of hospitalization when adjusted for Pra (probability of repeat admission score) but not when adjusted for Pra and physicians’ estimation of hospitalization probability (OR 0.62, p=0.002) but not when adjusted for Pra and physicians’ estimation of hospitalization probability (OR 0.6, p=0.16).

- Higher summary performance score
predicted lesser risk of hospitalization when adjusted for Pra (OR 0.68, p=0.004) and for Pra plus physician’s estimation (OR 0.79, p=0.05).

- Gait speed significantly predicted declines in functional status (Global Health score, p<0.001 for trend; Euroqol score, p=0.0039 for trend) and health status (for those with SF-36 ≥ 70 p=0.0101 for trend) over the 1-year follow-up.

**Comprehensive Assessment of Frailty (CAF)**

| Sündermann et al²⁹ | 1. HGS was measured using a hand dynamometer, and was adjusted for BMI and gender. | Each criterion is scored and incorporated into an overall CAF score with lower scores indicating less frailty. | 400 patients ≥ 74 years old undergoing elective cardiac surgery in a single center. | The AUC did not differ between the EuroSCORE (0.79), STS score (0.76) or CAF (0.71). The CAF correlated modestly with EuroSCORE (r=0.35) and STS. |
and was adjusted for gender and height.

3. Activity level was measured using a questionnaire regarding IADLs to calculate weekly kcal expenditure.

4. Standing balance was assessed by the amount of time individuals could stand a) with both feet together, b) feet in a semi-tandem position, c) feet in a full tandem position and d) make a 360 degree turn.

5. Body control was assessed by the time individuals could a) get up and down from a chair 3 times, b) pick up a pen from the floor and c) put on and remove a jacket.

mortality was compared to the Society of Thoracic Surgeons (STS) score, and the EuroSCORE.
6. Other: serum albumin and creatinine, and forced expiratory volume in one second

**Frailty Staging System**

Cacciatore et al

<table>
<thead>
<tr>
<th>Frailty Stage</th>
<th>Description</th>
<th>Prospective Study</th>
<th>HR for Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0-1 impairments = class 1</td>
<td>Prospective study of subjects &gt; 65 years old with (n=120) and without (n=1139) heart failure who were followed over 12 years.</td>
<td>- HR for death in fully adjusted analyses was 1.48 (95% CI 1.04 – 2.11) in patients with heart failure, and 1.36 (95% CI 1.17-1.57) in patients without heart failure.</td>
</tr>
<tr>
<td>2</td>
<td>2-3 impairments = class 2</td>
<td></td>
<td>- HR for death using frailty as a dichotomous variable (stage 3 versus stage 1) was 1.62 (95% CI 1.08 – 2.45) in patients with heart failure and 1.24 (95% CI 1.04 – 1.47) in those without.</td>
</tr>
<tr>
<td>3</td>
<td>4-7 impairments = class 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Disability, defined as a loss of ≥ 1 BADL.

2. Mobility disability, defined as inability to do heavy housework, walk up one flight of stairs or walk ½ mile.

3. Cognitive impairment, defined as mini-mental status exam (MMSE) score < 24.

5. Hearing impairment.

6. Total urinary incontinence.

Low social support.

**Frailty index based on the comprehensive geriatric exam (FI-CGA)**

<table>
<thead>
<tr>
<th>Jones et al. 33</th>
<th>1. Cognitive status</th>
<th>Domains 1-10 are each scored from 0 (no problem) to 2 (major problem) and summed with domain 11.</th>
<th>Secondary analysis of a clinical trial involving 169 frail, community-dwelling older adults in rural Nova Scotia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Mood and motivation</td>
<td>Compared to mild grade frailty, those with moderate and severe grade frailty had HR for death or institutionalization at 12 months of 1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Communication (vision, hearing and speech)</td>
<td>Compared to mild grade frailty, those with moderate and severe grade frailty had HR for death or institutionalization at 12 months of 1.9</td>
<td></td>
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</tr>
<tr>
<td>4. Mobility Based on natural cutpoints within the data set, the population was divided in to three grades of frailty:</td>
<td></td>
<td></td>
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<tr>
<td>5. Balance cutpoints within the data set, the population was divided in to three grades of frailty:</td>
<td></td>
<td></td>
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<tr>
<td>6. Bowel function data set, the participants were followed over 12 months.</td>
<td></td>
<td></td>
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<tr>
<td>7. Bladder function population was followed over 12 months.</td>
<td></td>
<td></td>
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<tr>
<td>8. ADLs and IADLs divided in to three grades of frailty: mild (FI-CGA 0-7), moderate (FI-CGA 8-13) and severe (FI-CGA &gt;13).</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>9. Number of comorbidities divided by 2.</td>
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<td></td>
</tr>
</tbody>
</table>

Mitinski et Frailty Indices similar For each Frailty 36,424 - The frailty indices
Index, deficits were summed and divided by the total number of deficits depending on what information was available from each dataset. Deficits were chosen based on 3 criteria:
1. The potential to accumulate with age
2. Does not saturate with age (i.e. become almost universal at a certain age, such as requiring correction for near vision), and,
3. Few missing data.

Higher scores indicate worse frailty.

Participants from 11 large population based studies in Canada, the United States, Sweden and Australia. 4 of these studies were clinical/institutional samples, however the frailty indices from the community-based samples were not closely correlated with age (r=0.985, p<0.001), however - At any given age, women had more deficits than men, yet women had lesser mortality compared to men for any given frailty index. - Risk of death increased exponentially with increasing Frailty Index scores.

The Canadian Study of Health and Aging Clinical Frailty Scale

Ekerstad et al

1. Very fit, each patient’s level of frailty (1-7) was assessed by consensus among a panel of 307 patients ≥ 75 years old
2. Well, without regular exercise was diagnosed with NSTEMI and associated with: - the
active disease treated as an inpatient. Follow-up was one month. The composite primary outcome of all-cause death, MI, revascularization, hospitalization, major bleeding, stroke, or need for dialysis (OR 2.17, 95% CI 1.28 – 3.67) – 1 month survival after adjustment for cardiovascular risk (OR 4.7, 95% CI 1.7 – 13.0)

**Edmonton Frail Scale (EFS)**

Dasgupta et al.

1. Cognition, evaluated with a clock draw
   - Higher EFS scores
   - 125 patients ≥ 70 years old
   - Independent

2. General health
   - indicating worse single, elective operative

Vulnerable, complain of being “slowed up” by disease

Mildly frail – limited dependence for IADLs

Moderately frail – limited dependent for both IADLs and ADLs

Severely frail – complete dependence for IADLs and ADLs or terminally ill
status, evaluated by number of hospitalizations in the past year. 3. Functional independence, as measured by ability to perform ADLs and IADLs. 4. Social support. 5. Use of ≥ 5 prescription medications per day. 6. Nutrition, as measured by recent weight loss. 7. Sad or depressed mood. 8. Incontinence. 9. Time to stand from a chair, walk 3 meters then return to the chair.

Frailty measures developed for one particular study.
Patients were defined as frail if they had any one deficiency in the Katz ADL Index, unable to ambulate independently or had a diagnosis of dementia. Patients were defined as frail if they had any one deficiency in the Katz ADL Index, were unable to ambulate independently or had a diagnosis of dementia.

Retrospective analysis of all patients undergoing cardiac surgery at the Queen Elizabeth II Health Sciences Centre between 2004 and 2007 (n=3,826).

Presence of frailty was an independent predictor of in-hospital mortality (OR 1.8, 95% CI 1.1–1.3), prolonged institutional care (OR 6.3, 95% CI 1.1–3.0) and mid-term mortality (HR 1.5, 95% CI 1.1–2.2).

Robinson et al\textsuperscript{40} studied, encompassing frailty, disability and comorbidity: These frailty, disability and comorbidity markers were used to create a clinical prediction rule for 6-month mortality and institutionalization.

110 patients ≥ 65 years old were followed. Sensitivity and specificity for predicting 6-month mortality and institutionalization were 81% and 86%, respectively if 4 out of the 6 following criteria were met:

1. Hematocrit < 35%  
2. Katz ADL index ≤ 6  
3. Mini-Cog < 4

1. Age mortality and institutionalization. were met:  
   1. Hematocrit < 35%  
   2. Katz ADL index ≤ 6  
   3. Mini-Cog < 4

2. Mini-Cog test (lower score indicates worse function)\textsuperscript{41}  
3. Chronic undernutrition
(weight loss of 10 lbs in past 6 months, BMI < 25 kg/m$^2$ and low albumin)

4. Number of falls in the last 6 months

5. Presence of depression

6. Hematocrit in the 30 days prior to surgery

Disability:

1. Katz ADL Index score (higher score indicates worse function).$^{39}$

Comorbidity:

1. Charlson Index (higher score indicates more comorbidity)$^{42}$

2. American Society of Anesthesiologists (ASA) score

4. Albumin $\leq$ 3.3 g/dl

5. $\geq$ 1 fall in past 6 months

6. Charlson Index $\geq$ 3
(higher score indicates higher surgical risk)\textsuperscript{16}

3. Polypharmacy – number of medications taken within the past 30 days prior to surgery

Muscle mass

Lee et al\textsuperscript{43} Measured the total cross sectional area of the bilateral psoas muscles at the level of the L4 vertebra. Total psoas muscle area (TPA) was analyzed both as a continuous variable and by tertiles. Retrospective study of 262 patients who underwent elective open abdominal aortic aneurysm repair.

- Kaplan Meier analysis showed the best 1- and 3-year survival in the top tertile of TPA (95\% and 91\%, respectively), compared to 87\% and 79\% for 1- and 3-year survival, in the lowest tertile of TPA.

- The effect of TPA on mortality is time dependent. HR for death for every 1000 mm\textsuperscript{2} decrease in TPA is 4.50 immediately post-operation, but
falls to 2.3 180 days after surgery.

CABG, coronary artery bypass graft; OR, odds ratio; CI, confidence interval; HR, hazard ratio; RR, risk ratio; HMO, Health Maintenance Organization; BMI, body mass index; ADL, activities of daily living; IADL, instrumental activities of daily living; CES-D, Center for Epidemiologic Studies Depression Scale; AUC, area under the curve; NRI, net reclassification index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; NSTEMI, non ST-elevation myocardial infarction; MI, myocardial infarction; ICU, intensive care unit

References


