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 left ventricular assist device (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, extrapulate 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.1,2 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.3 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.3 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.4,5 Measures of frailty, after adjustment for age and comorbidity, are highly predictive of death, incident disability, and hospitalization in patients with heart disease6–13 and those undergoing cardiac surgery.14–16 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,17,18 calculated 2-year actuarial survival in the HeartMate II DT trial was only 58%, and the rate of disabling stroke was 11% per year.1 Additionally, 5-year cost is estimated at $360 000.19 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 decade they were most commonly used.1,2 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 eligibility20 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.
Table 1. Existing Risk Models for Predicting Death or Adverse Outcome After LVAD Implantation

<table>
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<tr>
<th>Risk Score</th>
<th>Outcome(s) Predicted by the Risk Score</th>
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<td>222 patients receiving HeartMate XVE device as DT</td>
</tr>
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<td>Destination therapy risk score²⁴</td>
<td>90-d in-hospital mortality calculated from the following variables, each of which predicts worse mortality: platelets ≤148×10³/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 Abiomed (n=1) device</td>
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<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, Vg, XVE and II, Micromed-Debakey, Novacor, Thoratec percutaneous VADs and intravascular VADs</td>
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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). In addition, DT LVAD-eligible patients must be without significant noncardiac morbidity that would prevent meaningful postoperative improvement. Finally, LVAD therapy involves meticulous care of the percutaneous driveline site, system operation, anticoagulation, and frequent encounters with the healthcare system. 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. 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. The so-called “eyeball test,” 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, measures are varied, ranging from purely physical function to more extensive evaluations encompassing disability, comorbidity, and social vulnerability (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. 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). This suggests that carefully selected older adults can be appropriate for DT LVAD, 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. As such, frailty is an important component of

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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, blood pressure, body mass index, and hospitalization. In surgical patients, baseline frailty predicts postoperative morbidity, mortality, risk of institutionalization, 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 mortality 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 of reversible versus nonreversible frailty and has not examined it 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 >6,000 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 $\geq 65$ 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>Patients with heart failure(^{13})</td>
<td>4-y mortality</td>
</tr>
<tr>
<td></td>
<td>3. Self-reported exhaustion</td>
<td>Patients $\geq 65$ y status postpercutaneous coronary intervention(^{27})</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>4. Slow gait speed</td>
<td>Patients hospitalized for heart failure, minor stroke, pneumonia, or chronic obstructive pulmonary disease(^{10,11})</td>
<td>Longer hospital length of stay 1-y mortality Rehospitalization Incident disability</td>
</tr>
<tr>
<td></td>
<td>5. Low self-reported physical activity</td>
<td></td>
<td></td>
</tr>
<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 $\geq 70$ y old hospitalized for preexisting decompensated heart failure(^{6})</td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>2. Time taken to stand from a chair 5 times without using arms</td>
<td>Patients $\geq 70$ y old with significant coronary artery disease(^{7})</td>
<td>Major postoperative complication 6-mo mortality</td>
</tr>
<tr>
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<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>
<td>Gait speed</td>
<td>Component of both the Fried criteria and SPPB</td>
<td>Patients $\geq 70$ y old undergoing elective cardiac surgery(^{14})</td>
<td></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>Lee et al(^{15})</td>
<td>Frailty defined as</td>
<td>Cardiac surgery patients</td>
<td>In-hospital mortality</td>
</tr>
<tr>
<td></td>
<td>1. Any one deficit in Katz index for ADLs,(^{41}) and/or</td>
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<td>Prolonged institutional care</td>
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<td></td>
<td>2. Presence of dementia, and/or</td>
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<td>Midterm mortality</td>
</tr>
<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 $\geq 70$ 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>4. Mobility</td>
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<td>5. Balance</td>
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<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>
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<td></td>
<td>9. Need for help from nutrition or social resources</td>
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<td>10. No. of comorbidities</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 $\geq 74$ 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>2. Slow gait speed</td>
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<td>4. Low physical activity</td>
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<td>5. Poor standing balance</td>
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<td>6. Low serum albumin</td>
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<td>7. High brain natriuretic peptide</td>
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<td>8. Low forced expiratory volume in 1 s</td>
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(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-

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<td>Frailty Staging System</td>
<td>Each of the following domains is assessed and scored to form the Frailty Staging System score</td>
<td>Adults &gt;65 y old with and without heart failure⁹</td>
<td>12-y mortality</td>
</tr>
<tr>
<td></td>
<td>1. Disability</td>
<td></td>
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<td></td>
<td>2. Mobility</td>
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<td>3. Cognitive function</td>
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<td>4. Visual function</td>
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<td>5. Hearing function</td>
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<tr>
<td></td>
<td>6. Urinary continence</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>7. Social support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robinson et al⁴³</td>
<td>Preoperative variables divided into frailty, disability, and comorbidity categories</td>
<td>Adults ≥65 y old undergoing major elective abdominal surgery</td>
<td>The sensitivity (81%) and specificity (86%) of 6-mo mortality were maximized if 4 of 6 the following criteria were met before surgery</td>
</tr>
<tr>
<td></td>
<td>1. Age</td>
<td></td>
<td>1. Hematocrit &lt;35%</td>
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<tr>
<td></td>
<td>2. Mini-Cog test (lower score indicates worse function)⁴⁴</td>
<td></td>
<td>2. Katz ADL index ≥6</td>
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<td></td>
<td>3. Chronic undernutrition</td>
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<td>3. Mini-Cog &lt;4</td>
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<td></td>
<td>4. No. of falls in the last 6 mo</td>
<td></td>
<td>4. Albumin ≥3.3 g/dL</td>
</tr>
<tr>
<td></td>
<td>5. Presence of depression</td>
<td></td>
<td>5. ≥1 fall in past 6 mo</td>
</tr>
<tr>
<td>Edmonton Frail Scale (EFS)</td>
<td>Each of the following domains is assessed and scored to form EFS score</td>
<td>Adults ≥75 y old undergoing elective non-cardiac surgery⁴⁷</td>
<td>Postoperative adverse events (ie, cardiovascular or pulmonary complication, delirium, death, stroke, gastrointestinal bleed)</td>
</tr>
<tr>
<td></td>
<td>1. Poor cognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Greater no. of hospitalizations in the past year</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Inability to perform ADLs and IADLs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Lack of social support</td>
<td></td>
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<tr>
<td></td>
<td>5. Use of ≥5 prescription medications per day</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>6. Recent weight loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7. Sad or depressed mood</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8. Incontinence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9. Time required to stand from a chair, walk 3 meters, and then return to the chair</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADLs indicates activities of daily living; IADLs, instrumental activities of daily living.

Table 2. Continued

Flint et al Frailty and DT LVAD
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 multitystem 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.

Acknowledgments

We thank Joseph Cleveland, MD, for his careful review of the article and for offering his expertise regarding frailty in surgical populations.

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References

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Kelsey M. Flint, Daniel D. Matlock, JoAnn Lindenfeld and Larry A. Allen

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http://circheartfailure.ahajournals.org//subscriptions/
<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>Gait Speed</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></td>
<td>Gait speed 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, 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></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>
</tbody>
</table>
Hardy et al.\textsuperscript{5} Gait speed at usual pace over 4 meters

The \textit{a priori} definition of “clinically significant change” in gait speed was 0.1 m/s over 12 months. 487 community-dwelling patients \( \geq 65 \) years old from 2 primary care clinics (a Veterans Affairs clinic and a Medicare HMO clinic) were included. The 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)).

### Handgrip Strength (HGS)

Rantanen et al.\textsuperscript{6} Handgrip strength (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 were included. 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.
<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Participants</th>
<th>Follow-Up</th>
<th>Primary Findings</th>
</tr>
</thead>
</table>
| Rantanen et al\(^7\) | 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\(^2\), middle 20-24.99 kg/m\(^2\), largest > 25 kg/m\(^2\)). | 2900 initially healthy men aged 45-68 years followed for 30 years as part of the Honolulu Health Program. | - 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.  
|               |                                                                             |              |           | - 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\(^8\) | HGS was measured using a hand. HGS was analyzed by quartile (20-68).         | 140 non-disabled, Italian men, aged 20-68. |           | - Incidence of disability increased as                                                                                                               |
Klidjian et al.\(^9\) HGS 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. 225 patients undergoing major elective abdominal surgery whose HGS was < 85% normal of patients whose HGS was ≥ 85% of controls (p<0.001) experienced complications vs. 5% 45% of patients whose HGS was < 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.

Guo et al.\(^10\) 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 127 patients with previously untreated maxillofacial or oral cancers patients with HGS < 85% normal suffered significantly more major and minor complications than those with HGS ≥ 85% normal.
controls. (p=0.002).

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: 5,317 men and women ≥ 65 years old - 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).
   - 1-2 criteria met: recruited for the Cardiovascular Health Study (CHS) and
     - frail or prefrail
     - intermediate
   - ≥ 3 criteria met: frail

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

3. Exhausiton: Self-reported
exhaustion based on responses from 2 items on the CES-D questionnaire.\textsuperscript{13}

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 Fried criteria as

- 0 criteria met: This was a validation study for the Fried frailty, intermediate frailty and non-frailty criteria\textsuperscript{12} in 1002 disabled, community-cohorts (frailty)
- 1-2 criteria met: intermediate criteria\textsuperscript{12} in 1002
- ≥ 3 criteria met: dwelling women 11.3% vs 11.6%

BMI < 18.5 kg/m\textsuperscript{2}, frail aged ≥ 65 years intermediate 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).

43.8% vs 55.2% and non-frailty 44.9% vs 33.2%).

- Mortality, severe ADL disability and severe IADL disability were all significantly more common in frail and prefrail individuals compared to nonfrail individuals over a 3-year follow-up.

Makary et al15 Fried criteria as measured in Fried et al12 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.

• 0 -1 criteria met: robust or not frail
• 2-3 criteria met: university hospital clinic for elective surgery
• 4-5 criteria met: frail

- 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,\textsuperscript{16} the Lee score\textsuperscript{17} and the Eagle score\textsuperscript{18}; P<0.01)

Singh et al\textsuperscript{19} Fried criteria as measured in Fried et al\textsuperscript{12}

<table>
<thead>
<tr>
<th>≥3 criteria met:</th>
<th>Frail</th>
<th>≥ 3 criteria met:</th>
<th>Frail</th>
<th>≥3 criteria met:</th>
<th>Frail</th>
</tr>
</thead>
<tbody>
<tr>
<td>std. 0 criteria met:</td>
<td>not frail</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</td>
<td>not frail</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</td>
<td>not frail</td>
</tr>
<tr>
<td>- 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</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
| - Frailty added incremental prognostic value to the Mayo Clinic Risk Score in the prediction of death and MI (AUC
followed for 24 months. increased by 0.034, NRI 16%, p=0.038) but not death alone (AUC increased by 0.047, NRI 22%, p=0.13).

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. 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,
3) Injurious falls (HR 2.19, 95% CI 1.33 – 3.60)

**Short Physical Performance Battery (SPPB)**

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

- 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 those with summary performance scores of 10-12, those with 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**

SPPB was assessed as described in Guralnik et al. Gait speed measured over 4 meters was assessed

The study population was analyzed in quartiles of summary performance scores: 0, 1-4, 5-8 and 9-12.

All patients ≥ 65 years old admitted to two teaching hospitals in Italy with 9-12, mortality was
as a separate variable. decompensated, significantly higher in pre-existing heart failure. Patients were followed for a median of 1.2 years.

1. SPPB as described in Guralnik et al, 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, 7-9 fair, ≥ 75 years old, 10-12 good performance. Observational study of 7,250 community-dwelling women, followed for a mean of 3.8 years. In fully adjusted models, variables significantly predicting increased mortality included slower gait speed alone (p = 0.001 for trend), lower total summary performance score (p=0.02) and weaker HGS (p=0.01).

2. HGS was measured with a hand dynamometer in the dominant hand. The best of three trials was used (N/m²). Summary performance score was analyzed by tertile (0-4, 5-7, 8-12). Observational study of 92 patients ≥ 65 years old who - 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.27

- Slow gait speed predicted greater risk of hospitalization when adjusted for Pra (probability of repeat admission score)28 (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
continuous variable. or quality of life. 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 al\textsuperscript{29}

1. HGS was measured using a hand dynamometer, and was adjusted for BMI and gender.

2. Gait speed was measured at usual pace over 4 meters each criterion is scored and incorporated into an overall CAF score with lower scores indicating less frailty. The ability of CAF to predict 30-day mortality 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,\(^3^0\) and the EuroSCORE.\(^3^1\)
6. Other: serum albumin and creatinine, and forced expiratory volume in one second

**Frailty Staging System**

Cacciatore et al\(^{32}\) One point given for the presence of each of the following functions:

1. Disability, defined as a loss of \(\geq 1\) BADL.
2. Mobility disability, defined as inability to do heavy housework, walk up one flight of stairs or walk \(\frac{1}{2}\) mile.
3. Cognitive impairment, defined as mini-mental status exam (MMSE) score < 24.

- 0-1 impairments = class 1
- 2-3 impairments = class 2
- 4-7 impairments = class 3

Prospective study of subjects > 65 years old with (n=120) and without (n=1139) heart failure who were followed over 12 years.

- 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.

- 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.
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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Mood and motivation</td>
<td>analysis of a clinical trial with moderate and severe grade frailty</td>
</tr>
<tr>
<td></td>
<td>3. Communication (vision, hearing and speech)</td>
<td>involving 169 frail, community-dwelling older adults</td>
</tr>
<tr>
<td></td>
<td>4. Mobility</td>
<td>Based on natural cutpoints within the Nova Scotia. data set, the frailty population was divided in to three grades of frailty:</td>
</tr>
<tr>
<td></td>
<td>5. Balance</td>
<td>Compared to mild compared to mild grade frailty, those with moderate and severe grade frailty</td>
</tr>
<tr>
<td></td>
<td>6. Bowel function</td>
<td>Compared to mild compared to mild grade frailty, those with moderate and severe grade frailty</td>
</tr>
<tr>
<td></td>
<td>7. Bladder function</td>
<td>Compared to mild compared to mild grade frailty, those with moderate and severe grade frailty</td>
</tr>
<tr>
<td></td>
<td>8. ADLs and IADLs</td>
<td>Compared to mild compared to mild grade frailty, those with moderate and severe grade frailty</td>
</tr>
<tr>
<td></td>
<td>9. Needing help from nutrition or social resources</td>
<td>Compared to mild compared to mild grade frailty, those with moderate and severe grade frailty</td>
</tr>
<tr>
<td></td>
<td>10. Number of comorbidities divided by 2.</td>
<td>Compared to mild compared to mild grade frailty, those with moderate and severe grade frailty</td>
</tr>
</tbody>
</table>

Mitinski et Frailty Indices similar For each Frailty 36,424 - The frailty indices
In methodology to Jones et al\textsuperscript{33} were calculated from 11 different datasets 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.

Index, deficits were summed and divided by the total number of deficits considered. 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 or institutional samples and the remaining 7 were community-based samples. Deficits were closely correlated with age ($r=0.985, p<0.001$), however the frailty indices from the clinical/institutional samples were not correlated with age ($r<0.01, p>0.30$). 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\textsuperscript{35}

- Each patient’s level of frailty (1-7) was assessed by consensus among a 307 patients ≥ 75 years old diagnosed with NSTEMI and
- In multivariable analyses, frailty was independently associated with: - the...
active disease
3. Well, with treated comorbid disease 1 nurse, 1 physiotherapist, and 1 occupational therapist
4. Vulnerable, complain of being “slowed up” by disease
5. Mildly frail – limited dependence for IADLs
6. Moderately frail – limited dependent for both IADLs and ADLs
7. Severely frail – complete dependence for IADLs and ADLs or terminally ill

Edmonton Frail Scale (EFS)

Dasgupta et al.37
1. Cognition, evaluated with a clock draw
2. General health

Each item is scored from 0-1 or 0-2, with higher scores indicating worse
125 patients ≥ 70 years old undergoing a single, elective
- Higher EFS scores independently predicted post-operative

composite primary outcome of all-cause death, MI, revascularization,
Follow-up was one month.

- 1 month survival after adjustment for cardiovascular risk

(OR 4.7, 95% CI 1.7 - 13.0)
status, evaluated performance and non-cardiac complications (OR
by number of greater frailty. operation. 1.22 (95% CI 1.02 –
hospitalizations 1.46)).
in the past year - Clinically useful
3. Functional EFS score cut-points
independence, as were identified using
measured by likelihood ratios for
ability to perform adverse events.
ADLs and Therefore, very low
IADLs (<4) or very high (>7)
4. Social support EFS scores may be
clinically useful for
5. Use of ≥ 5 predicting patients at
prescription low (OR 0.27, 95% CI
medications per 0.09-0.80) or high
day. (OR 5.02, 95% CI
measured by operative risk,
recent weight respectively.
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
Lee et al\textsuperscript{38} 1. Katz ADL index\textsuperscript{39} (i.e. dependence in feeding, bathing, dressing, transferring, toileting or urinary incontinence).

2. Ability to ambulate independently

3. Diagnosis of dementia from a trained specialist

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} Pre-operative markers 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 included. Sensitivity and specificity for predicting 6-month mortality 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

Pre-operative markers studied, including age, Mini-Cog test (lower score indicates worse function)\textsuperscript{41}, chronic undernutrition.
(weight loss of 10 lbs in past 6 months, BMI < 25 kg/m² 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 ≤ 3.3 g/dl

5. ≥ 1 fall in past 6 months

6. Charlson Index ≥ 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


