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Moving the Field Forward: Untangling the Impact of Frailty on Patients With Advanced Heart Failure and on Prognosticating Outcomes

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The study of frailty and its effect on patients with heart failure (HF) has undergone significant growth in recent years. The definition of frailty is complex and refers to older patients with multiple comorbidities and reduced functional capacity, resulting in increased vulnerability to stressors and decreased physiological reserve.[1] Estimates of the prevalence in HF are high but vary widely, from almost half to nearly 80%,[2] which is probably due to the fact that the clinical manifestations of both, including myocardial and metabolic failure, remain challenging to tease apart. For example, the Cardiovascular Health Study found that frailty was most strongly associated with HF rather than with any other forms of cardiovascular disease, independent of age or New York Heart Association class. They demonstrated that the relationships among frailty, comorbidity and disability predicted and/or exacerbated each other.[3] Several scoring indices have been employed in the attempt to use more quantitative metrics for frailty, such as slow gait speed and weak grip strength.[1,2,4] Ultimately, the goal is to further understand which symptoms are potentially reversible with goal-directed medical therapy and how frailty can affect prognosis in those with advanced HF following advanced therapies, including heart transplantation and left ventricular assist device placement.[1]

In this study, Lala et al. developed an adaptation of the Fried Frailty Phenotype, the most widely adopted frailty model currently available.[5] The authors coined their model the HF-Fried Frailty Criteria, including 5 components: (1) weakness with handgrip strength; (2) slowness with 15-foot walk speed; (3) weight loss; (4) inactivity; and (5) exhaustion, based on the Kansas City Cardiomyopathy Questionnaire.[6] Each component scored a point, summing to a total score, with subjects divided into 3 frailty categories: nonfrail (≤ 1 point), prefrail (2 points) or frail (≥ 3 points). They hypothesized that applying the HF-Fried Frailty Criteria to ambulatory patients with advanced HF would be associated with the 1-year composite outcome of durable mechanical circulatory support, heart transplantation or death. The patient population was obtained from the REVIVAL study, a prospective, observational cohort study of ambulatory patients with advanced systolic HF from 21 U.S. heart transplant/mechanical circulatory support centers from July 2015 to June 2016–a total of 345 patients with data for all 5 components. The authors found that frailty was

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present in 17%; prefrailty in 40%; and no frailty in 43%, with 67% meeting criteria based on inactivity and 54% for exhaustion. Frail and prefrail patients had an increased risk of the primary composite outcome compared to nonfrail patients. More broadly speaking, the HF-Fried Frailty Criteria had modest predictive power in identifying ambulatory patients with advanced HF at high risk for advanced therapies or death at 1 year, driven primarily by assessments of inactivity and exhaustion.[6]

Currently, there are multiple frailty scores for a more general patient population, but none have been validated in a population of people with HF. Such scores include the Frailty Phenotype, the Deficit Accumulation Index, the Tilburg Frailty Indicator, the Comprehensive Geriatric Assessment, the Frailty Staging System, the Canadian Health and Ageing Clinical Frailty Scale, and the Survey of Health, Ageing and Retirement in Europe Frailty Index.[1] Similarly, others have tried to use or adapt these models.[2,7,8] For example, FRAIL-HF, a prospective cohort study of 450 patients aged ≥ 70 years who had been hospitalized for HF, evaluated the relationships between the frailty phenotype and associated issues (ie, comorbidities, coexistent geriatric syndromes, self-care, and social support) with clinical, functional and quality-of-life outcomes. The study found that even in nondependent patients, frailty was a risk factor for early disability, long-term mortality and hospital readmission.[4] Sze, et al. applied several frailty screening and assessment tools to 467 ambulatory patients with HF compared with 87 control patients and also found that frailty was associated with increasing age, comorbidities and HF severity. They concluded that a simple screening tool identified similar groups as well as more lengthy assessment models identified them. Another recent prospective study of patients with HF assessed the impact of gender, also using the Fried Frailty Index, as well as dyspnea, sleep-related impairment, pain interference, depression, and anxiety. The authors also measured body composition with dual-energy radiograph absorptiometry and found that frailty was characterized by comorbidities and worse HF symptoms, and women tended to be more physically frail than men.[9]

In this context, the study by Lala et al. ultimately provides similar conclusions. Commendably, the authors took an important step by striving to quantify the impact of frailty on outcomes related to advanced therapies. Doing so pushes the field forward by attempting to adapt a well-validated frailty score specifically for patients with HF. The authors quantified the predictive power of each of the 5 components and found, specifically, that the more subjective patient-reported components had the strongest predictive power, which was still only modest, at best. In addition, Lala and colleagues assessed the concept of prefrailty in this HF population and how it correlated with outcomes, finding that it confers increased risk of HF progression—once again tackling an important, yet poorly understood, entity in this patient population.

However, the HF-Fried Frailty Criteria must be interpreted within the context of some limitations acknowledged by the authors. Most notably, the original Fried Frailty Index was developed in an older patient population with a low prevalence of HF (4.0%), let alone advanced HF.[10] The authors also point out that few patients met the weight-loss criteria, and it stands to reason that perhaps another metric should be employed to capture malnutrition or loss of muscle mass because patients with advanced HF are subject to frequent weight

fluctuations due to volume status. In addition, the original Fried questionnaire used to assess inactivity detailed activities, such as jogging or bowling, which are not relevant to the majority of ambulatory patients with advanced HF, so the authors employed aspects of the Kansas City Cardiomyopathy Questionnaire questionnaire. In addition, the HF Fried Frailty Criteria was not first internally validated prior to use but, rather, was based on expert opinion and assumptions derived from prior studies.

In moving forward, given the limited predictive power of the model, further work is needed to better quantify the impact of underlying frailty on outcomes in patients with advanced HF. These results suggest that frailty, as defined by this modified Fried frailty score, does not stratify precisely the risk that younger patients with advanced HF will need advanced therapies or will die. This may reflect the unique pathophysiology, hemodynamic and perfusion consequences seen in advanced HF, including systemic inflammation, abnormalities in skeletal muscle and high comorbidity burdens.[5] In taking these results a step further, we need better understanding of why the components of inactivity and exhaustion were more predictive, especially because they are both subjective measures in a disease state with a well-established symptomatic burden. Are these symptoms truly targeting the concept of frailty, or are they merely related to advanced HF disease? Others have argued for a multifaceted approach, including not only physical function, but also medical, cognitive and social components.[5] The work of Lala et al. echoes prior work in the field, confirming that the presence of frailty portends a worse prognosis, but it also highlights the nuances of defining frailty in patients living with the intricate physiologic derangements seen with advanced HF.

Thus, the time may be right to generate a new definition of frailty that is tailored specifically to the complex advanced HF phenotype. Building upon the predictors that have shown promise, a de novo derivation of a unique frailty score specifically for those with advanced HF may yield improved prognostic performance and greater clinical utility. Importantly, this work has paved the way for future work toward an HF-focused frailty score that would provide quantifiable and actionable data for advanced therapy evaluations. Additionally, once the concept of frailty in advanced HF is better defined, it can inform the study of broader populations of patients with HF, including those without advanced disease or who are prefrail. This will be crucial for delineating the potential impact of the growing goal-directed medical therapy armamentarium of efficacious HF therapies (including angiotensin receptor-neprilysin inhibitors and sodium-glucose cotransporter-2 inhibitors) on frailty. A small retrospective study of 37 patients awaiting heart transplantation recently suggested an effect of these therapies on frailty, demonstrating that treatment with an angiotensin receptor-neprilysin inhibitor was associated with improvement in physical frailty.[11]

In summary, although many questions remain unanswered, the study by Lala et al. provides key insights for a shift toward a more HF-specific frailty paradigm. One future objective is that, by more accurately defining and capturing frailty in patients with advanced HF, we can improve risk-stratification approaches in this clinically challenging and heterogeneous population. As the definition of frailty in advanced HF evolves toward a more precise phenotype, clinician investigators will be armed with a better tool for identifying frailty in their patients and studying the impact of frailty on person-centered outcomes. We have only

skimmed the surface of understanding frailty in HF, but we've gotten a clear glimpse of what may be on the horizon.

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