CONSENSUS STATEMENT

ASSESSING AND MANAGING FRAILTY IN ADVANCED HEART FAILURE: AN INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION CONSENSUS STATEMENT

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ABSTRACT

Frailty is increasingly recognized as a salient condition in patients with heart failure (HF) as previous studies have determined that frailty is highly prevalent and prognostically significant, particularly in those with advanced HF. Definitions of frailty have included a variety of domains, including physical performance, sarcopenia, disability, comorbidity, and cognitive and psychological impairments, many of which are common in advanced HF. Multiple groups have recently recommended

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incorporating frailty assessments into clinical practice and research studies, indicating the need to standardize the definition and measurement of frailty in advanced HF. Therefore, the purpose of this consensus statement is to provide an integrated perspective on the definition of frailty in advanced HF and to generate a consensus on how to assess and manage frailty. We convened a group of HF clinicians and researchers who have expertise in frailty and related geriatric conditions in HF, and we focused on the patient with advanced HF. Herein, we provide an overview of frailty and how it has been applied in advanced HF (including potential mechanisms), present a definition of frailty, generate suggested assessments of frailty, provide guidance to differentiate frailty and related terms, and describe the assessment and management in advanced HF, including with surgical and nonsurgical interventions. We conclude by outlining critical evidence gaps, areas for future research, and clinical implementation.

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KEYWORDS:
heart failure; mechanical circulatory support; heart transplantation; frailty

INTRODUCTION

Frailty is increasingly recognized as a salient condition in patients with heart failure (HF), particularly in those with advanced HF (i.e., refractory symptoms despite optimal medical and device therapy[1]). Both conditions are prevalent, especially with aging, and both adversely affect prognosis. It is estimated that approximately 50% of patients with HF are frail[2]; however, estimates vary widely across studies due to differences in subpopulations (e.g., community-dwelling vs advanced HF) and differences in frailty assessment tools utilized.[3] Frailty is also strongly associated with worse outcomes in HF. Meta-analyses have demonstrated that frailty in HF is associated with a roughly 50% higher risk of both hospitalization and mortality compared with nonfrailty.[4,5] Multiple studies have also shown that frailty is associated with worse symptoms (e.g., dyspnea) and quality of life in patients with HF.[6,7] Frailty is especially common in patients with advanced HF[3] and affects the prognosis in those undergoing orthotopic heart transplantation (OHT)[8] and left ventricular assist device (LVAD) implantation.[9,10] For example, frail patients undergoing LVAD surgery experience prolonged intubation and ventilatory support, increased length of hospital stay, and higher risk of delirium and postdischarge mortality compared with nonfrail patients.[11] Given the clinical significance of frailty in HF, frailty assessments warrant further investigation and integration into the clinical practice of patients with advanced HF.

A number of organizations and statements have advocated using frailty assessments when caring for patients with advanced HF.[12,13] For example, the 2016 International Society for Heart and Lung Transplantation (ISHLT) Updated Guidelines for Listing Criteria for Heart Transplantation recommended frailty assessments as an important component of the selection process.[14] However, they noted that "the lack of standardization makes using frailty as definitive criteria for listing difficult." The American Society of Transplantation provided a consensus statement on frailty in heart transplantation and noted a need to develop objective frailty assessment tools for risk stratification.[15] Moreover, there is emerging evidence that frailty and its associated risk may be reversible with advanced therapies (e.g., LVAD, OHT)[16] and/or rehabilitation (or possibly prehabilitation) programs.[17,18]

A major barrier to incorporating frailty assessments into clinical practice is that the definition and measurement of frailty in HF are not standardized. Past assessments have included a variety of domains, including physical performance, sarcopenia, disability, comorbidity, cognitive dysfunction, and psychological disorders. But these domains are also often highly prevalent in advanced HF,[19,20] which creates conceptual confusion. Moreover, as frailty is considered a "geriatric" condition, there is confusion on how to formulate definitions and assessment tools for a population that spans a wide age spectrum.[21] To address this need, several groups have presented position or consensus statements on the definition, assessment, and implementation of frailty among adults with HF in general,[22] among older adults with HF,[23] and in heart transplantation.[15] However, frailty assessments remain underutilized across advanced HF clinical settings despite a strong evidence base, and there remains a need to standardize recommendations for advanced HF practices across the world. To address this gap, the ISHLT convened a writing group to focus specifically on frailty among those with advanced HF, a subpopulation that is highly frail but with potential for reversibility with advanced therapies and other modalities (e.g., rehabilitation). Thus, the purpose of this consensus statement is to provide an integrated perspective on the definition of frailty in advanced HF and to generate a consensus on how to assess and manage frailty.

In developing this consensus statement, the authors were subdivided into groups that were assigned the task of reviewing the published evidence for each of the major sections of the paper. The writing group as a whole was convened at 3 virtual meetings between September 2021 and March 2022 to discuss progress, review sections, and generate and discuss recommendations. Each group's contribution was then combined by the project leaders to generate a consensus statement. Following external review and further input from the group over email correspondence, we generated this final consensus statement, which has been approved by the entire writing group.

GENERAL CONCEPTUALIZATION AND ASSESSMENT OF FRAILTY

Conceptualization of frailty

While the term frailty has been familiar to clinicians for a long time, there has been variability in its conceptualization and measurement. To date, 2 major approaches have emerged to capture this syndrome: physical frailty (largely driven by Fried's "Frailty Phenotype Criteria") and multidimensional frailty (largely driven by Rockwood's "Frailty Index"). Traditionally, these approaches have been "disease agnostic" and applied to chronological aging.

First conceptualized 2 decades ago, the Frailty Phenotype Criteria characterize frailty as a cycle in which deficits in multiple systems, including the musculoskeletal, neuroendocrine, nutritional, and immunologic systems, combine to produce a clinical syndrome associated with increased vulnerability to stressors.[24] Fried et al defined frailty as "a biologic syndrome of decreased reserves and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes." While minor adaptations have been made to the wording over the years, this definition has largely remained unchanged in the geriatric literature. The phenotype is defined by 5 components including weight loss, weakness, slowness, low physical activity, and exhaustion.[24] This approach classifies an individual as being frail when 3 of 5 criteria are met, and prefrail and nonfrail (robust) when 1 to 2 and 0 criteria, respectively, are met.[24]

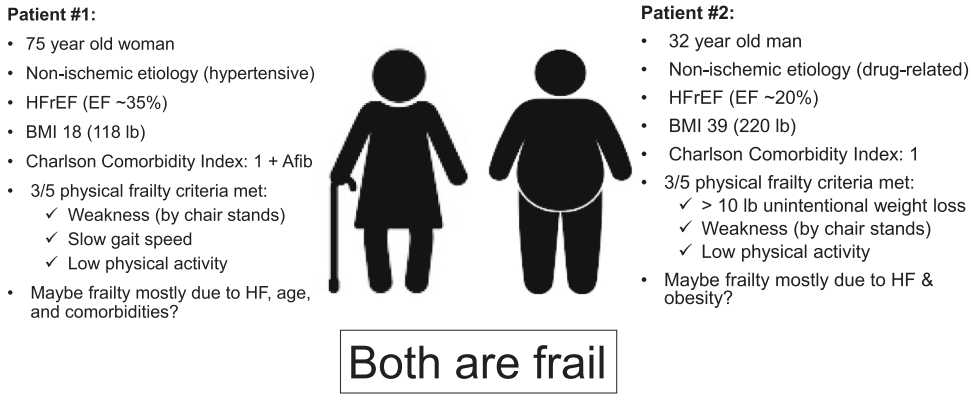
The second major conceptualization of frailty is termed the "Frailty Index" by Rockwood and colleagues, who developed it as a cumulative aging-related deficit model.[25,26] In this multidimensional model, frailty is the sum of aging-related deficits encompassing functional impairments, biochemical abnormalities, symptoms, signs, and comorbidities. The Frailty Index is a ratio of the actual deficits to the total number of deficits assessed (typically somewhere between 30 and 70).[27] Updated approaches, largely based on the related Clinical Frailty Scale, have been published.[28,29]

Tools for assessing frailty

Despite these conceptualizations, frailty is often identified without standardized screening or assessment tools. For example, clinicians will label a patient frail using the so-called "eyeball test."[30] However, frailty assessment based on visual impression is unreliable and influenced by location of assessment, time of the day, nutritional status, mood, volition, and presence of sleep disturbances.[31-34] Moreover, frailty is present across age and weight spectrums (Figure 1 as example in HF), making the "eyeball test" unreliable. Because of these limitations, over 60 frailty screening and assessment tools have been developed.[35]

In an ideal setting, frailty assessment tools should have the ability to differentiate reversible from irreversible frailty, and inform clinicians about the risks of morbidity and mortality with various therapies. [20] However, no single frailty assessment tool has proven superior in all clinical situations. Of the available tools, the Frailty Phenotype Criteria and the Frailty Index have been the most widely applied.[35] Notably though, these approaches have been modified to various degrees depending on the study procedures and available data. For example, chair stands replacing grip strength measurements in the Frailty Phenotype Criteria[36] or assessments that determine frailty solely based on a single criterion (e.g., gait speed[37] or grip strength[38]). As a fully self-report alternative, the 5-item FRAIL (fatigue, resistance, ambulation, illness and loss of weight) scale[39] is a derivative of the Frailty Phenotype Criteria that offers improved practicability but requires further validation. In contrast, the Frailty Index is intended to be adaptable depending on the availability of data.[25] This approach works well with existing datasets (e.g., electronic medical record, completed clinical trials, registries) when frailty needs to be quantified retrospectively.

Figure 1 Comparison of 2 frailty phenotypes in heart failure. Frailty affects many adults with heart failure across the lifespan, spectrum of heart failure severity, and weight range, presenting difficulties with management of frailty. BMI, body mass index; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



However, the Frailty Index has been used with 30 to 70 criteria, which makes standardization difficult. Other assessment tools[35,40,41] have also been widely used (Table 1 as examples in HF).

Choosing the most appropriate frailty assessment tool may depend on its intended use. For example, some evidence suggests that compared with physical frailty tools, multidimensional frailty assessments may be more effective and informative in risk stratification and more accurate in mortality prediction.[42] However, multidimensional tools can become overly complex, hindering the ability to track frailty. Also, the cumulative frailty score does not identify specific deficits that may be reversible, especially since comorbidities rarely disappear entirely. On the other hand, the Frailty Phenotype Criteria may better ascertain reversibility of frailty with targeted interventions. Additionally, frailty screening tools are available for risk stratification or rapid outpatient screening; but a formal in-depth assessment of frailty may be necessary to define a specific, individualized management plan to optimize the patient's condition and reduce potential risk for complications.[43]

POTENTIAL MECHANISMS OF FRAILTY IN ADVANCED HEART FAILURE

Neurohormonal activation, immunosenescence, inflammation, and skeletal muscle and adipose tissue dysfunction are all associated with both HF and frailty and may all be targets to reverse frailty (Table 2).[44] As HF advances, these overlapping characteristics may become even more pronounced, particularly when coupled with comorbidities. It is often difficult, however, to determine which comes first: frailty or HF.[21,45] It has been shown that those who are prefrail or frail are more likely to develop HF than those who are not frail.[46,47] Similarly, some nonfrail patients with HF develop frailty in the course of the disease; although incident frailty among patients with an established diagnosis of HF has not been studied. Thus, frailty may precede or follow a diagnosis of HF, and when confronted with a patient with both, it is often uncertain whether frailty will resolve with HF treatment modalities.

Neurohormonal activation

Chronic neurohormonal activation, including autonomic dysfunction and impaired hemodynamics, is a feature of both HF[48] and frailty,[49,50] potentially contributing to wasting syndromes such as cachexia.[44] For example, the balance between sympathetic and parasympathetic activation is disrupted in both frailty[51–53] and HF,[54,55] as reflected by reduced heart rate variability, indicating increased sympathetic activity and reduction of parasympathetic activity. Hemodynamic abnormalities in HF, including reduced cardiac output and chronic congestion, along with concomitant mitochondrial abnormalities impair oxygen utilization and exercise tolerance in HF.[56] Diminished oxygen delivery to skeletal muscle contributes to downregulation of anabolic pathways and upregulation of catabolic pathways, resulting in decreased muscle mass and weight loss in HF and potentially cachexia.[57-59] Thus, hemodynamic dysfunction may, in part, exacerbate a frailty phenotype. In a small sample of

Table 1 Commonly Used Frailty Assessment Tools in Heart Failure.[a]

Tool and country of origin	Measurement settings	Type of measurement	Domains				No. of items	Scoring system	Considerations for patients with heart failure
			Physical	Psychological	Cognitive	Other			
Clinical Frailty Scale (CFS) version 1.0[93] version 2.0[171] Canada	Clinical settings	Clinical judgment based on a written description of frailty, complemented by a visual chart	X (exercise and physical activity)			Comorbidities Activities of daily living	1	Visual and written graph for frailty with 9 graded pictures varying from a level of 1 (very fit) to 8 (living with very severe frailty) or 9 (terminally ill but no otherwise living with severe frailty). Frailty is diagnosed with a score ≥5.	Central tenet is to summarize the overall level of fitness of frailty of an older adult; relies solely on a provider's subjective evaluation; not valid for younger patients and those with "stable single-system disabilities"[171]; may also create a "ceiling effect" in older patients with advanced HF. Example in HF: Sze et al (2019)[90]
Essential Frailty Toolkit (EFT)[42] Canada	Clinical settings	Performance-based, cognitive assessment, medical record review	X (chair stands, albumin, hemoglobin)		X		4	Each criterion is 1 point (except 2 points for unable to perform chair stands) 0 criteria met = non-frail; 1-2 criteria met = pre-frail; 3+ criteria met = frail	While widely used and validated among patients with valvular disease and those undergoing coronary artery bypass surgery; it has not been tested in advanced HF. Example in aortic valve replacement: Afilalo et al (2017)[42]
Fatigue Resistance Ambulation Illness Loss of Weight (FRAIL) Scale[39] USA	Clinical settings or population screening	Self-report	X (fatigue, difficulty walking, weight loss questions)			Comorbidities	5	0 criteria met = nonfrail; 1-2 criteria met = prefrail; 3+ criteria met = frail	Further validation is needed for both hospitalized and community-dwelling patients with advanced HF Example in HF: DeGroot et al (2023)[92]
Frailty Index (FI)[25] Canada	Population screening	Uses available data, usually derived	X (possibly)	X (possibly)	X (possibly)	Comorbidities Activities of daily living symptoms	30-70	Calculated by dividing the number of deficits present by	Shown good utility to identify frailty retrospectively (e.g., in clinical

Continued

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Tool and country of origin	Measurement settings	Type of measurement	Domains				No. of items	Scoring system	Considerations for patients with heart failure
			Physical	Psychological	Cognitive	Other			
		from medical record, but may include performance tests						the total number considered. Ratio reported as a continuous variable (range 0-1) with scores >0.25 typically indicative of frailty	trials) or using electronic medical records, but it may be less informative in identifying reversibility of frailty and specific interventions to target frailty. Examples in HF: Dunlay et al (2014)[87]; Sanders et al (2018)[172]; Pandey et al (2022)[88]
Frailty Phenotype Criteria[24] USA	Clinical settings	Combination of performance tests and self-report	X (weight loss, grip strength or chair stands, gait speed, self-reported exhaustion and low physical activity)		X (sometimes added on)		5	0 criteria met = nonfrail; 1-2 criteria met = prefrail; 3+ criteria met = frail	Widely used and validated in advanced HF, but limitations have included the impractability of performing some of the measures in clinical settings, complicated cut points depending on sex and height, and multiple modifications. Examples in HF: Tanaka et al (2018)[173]; Rodriguez-Pascual et al (2017)[174]; Pandey et al (2019)[94]; Jha et al (2017)[9]
Gait Speed[175] Multinational	Clinical settings	Performance test	X (gait speed)				1	Calculated by dividing the distance walked (typically 4-8 m) by the time it takes to walk that distance (in seconds); typically >0.8-1.0 m/s is	While highly predictive, it only captures 1 physical component of frailty. Examples in HF: Pulignano et al (2016)[176]; Cooper et al (2017)[177]

Continued

Table 1 Commonly Used Frailty Assessment Tools in Heart Failure.[a]

Tool and country of origin	Measurement settings	Type of measurement	Domains				No. of items	Scoring system	Considerations for patients with heart failure
			Physical	Psychological	Cognitive	Other			
								considered slow	
Short Physical Performance Battery (SPPB)[178] USA	Clinical settings	Performance tests	X (balance test, gait speed, chair stands)				3	Scores range from 0-12 depending on performance on 3 tests: walk test, 5 repeat chair stands, standing balance	Widely used and validated across multiple contexts, but in HF, it is typically assessed alongside another frailty measure. Also, it may not be feasible or too time-intensive to perform in clinical settings and focuses on lower extremity function only. Examples in HF: Chiarantini et al (2010)[179]; Pandey et al (2019)[94]; Kitzman et al (2021)[180]
Survey of Health, Ageing, and Retirement in Europe-Frailty Instrument (SHARE-FI)[181] Europe	Clinical settings or population screening	Combination of performance tests and self-report	X (appetite, gait speed, grip strength, exhaustion, physical activity)				5	0 criteria met = nonfrail; 1-2 criteria met = prefrail; 3+ criteria met = frail	A valid alternative based on the Frailty Phenotype Criteria to rapidly assess frailty in primary care; limited validation in advanced HF. Example: McDonagh et al (2020)[83]
Tilburg Frailty Indicator (TFI)[182] The Netherlands	Clinical settings or population screening	Self-report	X	X	X	Social questions	15	A score of ≥5 indicates frailty	While it has been used among community-dwelling patients with HF and older adults, it has not been tested in advanced HF Example: Uchmanowicz et al (2015)[183]

Abbreviations: HF, heart failure

[a]Please see article by Ijaz et al for a comprehensive list of available assessments of frailty in cardiovascular disease.[184]

Table 2 Pathophysiology of Frailty in Advanced Heart Failure.

Biological/physiological process	Pathological mechanisms	Manifestations	
		Specific	Overall
Neurohormonal activation	Renin-angiotensin-aldosterone system activation Sympathetic nervous system activation Autophagy pathway activation Natriuretic peptide system activation Reduced parasympathetic tone	Impaired cardiac function and peripheral vascular vasoconstriction Reduced skeletal muscle mass and function	Frailty presentation, leading to: Worse symptoms Diminished quality of life Loss of functional independence Hospitalization Death
Immunosenescence	Immune cell dysfunction and dysregulation Increased pro-inflammatory mediators Decreased response to immunogenic stimuli Systemic, low-grade "sterile" inflammation	Decreased risk of rejection Increased susceptibility to infections and malignancy post cardiac transplantation	
Inflammation	Systemic low-level chronic inflammation Increased levels of pro-inflammatory biomarkers	Fatigue Anemia Enhanced catabolic state Cachexia	
Skeletal muscle dysfunction	Decrease in muscle mass, strength, and function Change in muscle composition (fiber type, capillary circulation, and adipose content)	Sarcopenia and cachexia Weakness Fatigue Reduced exercise capacity Impaired physical function	
Adiposity and adipose tissue dysfunction	Dysregulated cytokines from adipose tissue (adipokines) Systemic low-level chronic inflammation Dysfunctional metabolic activity of fat	Increased fatty deposition in muscle mass Sarcopenic obesity	
Insulin resistance	Pro-inflammatory state causing metabolic impairment	Reduced exercise tolerance Weakness	

adults with HF undergoing a right heart catheterization, lower cardiac output and higher heart rate were associated with physical frailty independent of other clinical factors.[36] Among patients with advanced HF, LVAD implantation or heart transplantation has improved levels of frailty in many patients suggesting that impaired hemodynamics contribute to frailty, and in turn frailty can be reversible with improved hemodynamics.[16,60] However, this reversibility is not seen in all patients, implying that there are other nonhemodynamic factors that contribute to frailty in HF.[10]

Immunosenescence and inflammation

Immunosenescence refers to age-related alterations in the immune system,[61] resulting in increased proinflammatory mediators in the absence of an obvious trigger and decreased inflammatory response to immunogenic stimuli.[57,62,63] Possible aging-related triggers include damaged cells, failure of dysfunctional neutrophils and macrophages to properly remove cellular debris, and a growing number of senescent cells secreting proinflammatory cytokines.[62,63] The proinflammatory state associated with frailty may contribute to some of the pathophysiology of HF; however, causality is hard to establish as HF alone is similarly associated with elevation in markers of inflammation[57,63] such as interleukin-6, tumor necrosis factor-α, interferon-γ, and C-reactive protein.[15,57,63,64] Moreover, increased inflammation can result in decreased

serum albumin, a marker of both frailty[63] and advanced HF.[8] Given that increasing age is associated with frailty and HF, proinflammatory processes associated with aging could serve as a link between these conditions.[15,57]

Skeletal muscle and adipose tissue dysfunction

Intact neuroendocrine and immune systems are prerequisites for maintaining muscle mass and muscle homeostasis, through a balance of new muscle cell production, hypertrophy of muscle cells, and muscle cell protein loss.[65] A reduction in muscle cell formation and catabolism leads to sarcopenia, with exaggerated loss of muscle strength, mass, and function beyond the normal aging process.[15,64,66] Promoting factors for loss of muscle mass and performance, including high levels of inflammatory cytokines, low levels of anabolic hormones, micronutrient deficiencies, and physical inactivity, are prevalent in frailty and HF.[15,64,66] As a result, both HF and frailty are associated with altered skeletal muscle composition, including high levels of adipose tissue in skeletal muscle, changes in skeletal muscle fiber type, lower capillary density, and anabolic resistance of muscle proteins to stimuli, which contribute to decreased mitochondrial function and reduced exercise capacity.[66,67]

Adipose tissue dysfunction, which is common in HF[68] and related comorbidities (e.g., obesity, diabetes, insulin resistance), is likely an additional mechanism involved in the development of frailty in advanced HF.[69,70] For example, central obesity has been associated with a chronic proinflammatory state; in turn, an increase in cytokines (i.e., adipokines) contributes to an increase in both proinflammatory mediators and cellular debris.[67,71] Moreover, elevated adipose levels in and around skeletal muscle further promote a proinflammatory, insulin-resistant state, and sarcopenia through paracrine and endocrine actions.[65,66] The resulting sarcopenic obesity contributes to decreased muscle performance, impaired physical function, and increased frailty.[66,67,71] Another hormonal factor, ghrelin, which stimulates appetite along with other anabolic properties, is increased among patients with HF and cachexia.[72] Ghrelin was associated with increases in growth hormone and tumor necrosis factor-α suggesting a compensatory mechanism in the setting of catabolic-anabolic imbalance.[57,73] Finally, 1 exploratory study showed that markers of adipose and skeletal muscle function, specifically adiponectin, insulin-like growth factor, and myostatin, were significantly lower among frail compared with non-frail adults with HF.[74]

Intersection of comorbidities, frailty, and advanced heart failure

Based on the above pathophysiological mechanisms, it is not surprising that comorbidities[75] likely impact the development and trajectory of frailty in advanced HF.[1,76] The accumulation of deficits across multiple organ systems leads to the dysregulation of homeostasis and loss of physiological reserve.[77] The majority of comorbidities, such as chronic kidney disease, chronic obstructive pulmonary disease, and diabetes mellitus, are proinflammatory and linked to changes in muscle composition, sarcopenia, and insulin resistance as discussed above.[67] Therefore, the adverse effects of advanced HF, aging, and comorbidities on physical functioning and other clinical health outcomes are cumulative and potentially synergistic. The relative contributions of comorbidities vs HF to the pathophysiological mechanisms of frailty, however, are not well-understood and are beyond the scope of this paper.

PROPOSED WORKING DEFINITION OF FRAILTY IN ADVANCED HEART FAILURE

Based on the evidence to date, we propose a working definition of frailty in advanced HF, as follows: *A distinct biologic syndrome of declines across multiple physiological systems that may occur either independently or are potentiated by advanced HF, resulting in decreased reserves and increased vulnerability to stressors, and it is potentially reversible with a combination of cardiovascular and/or non-cardiovascular therapies.*

FRAILTY CONCEPTUALIZATIONS AND ASSESSMENTS IN ADVANCED HEART FAILURE

Background

There has been growing interest in the intersection of frailty with HF stemming from (1) a need to improve upon the "eyeball test,"[31] (2) the important effect of frailty on HF prognosis,[4] (3) a need to discern the causes of frailty in HF (e.g., aging, HF, and/or comorbidity driven frailty)[21] in order to determine appropriate interventions, (4) the desire to ascertain reversibility of frailty, and (5) the need to test interventions to reverse frailty.[10,21] In fact, the number of publications with the terms "frailty" and "heart failure" has grown exponentially in just a decade from 34 publications in 2012 to 533 publications in 2022 (source: Scopus). To summarize the evidence to date on HF and frailty: (1) approximately 45% to 50% of patients with HF are likely considered frail,[2,4] (2) although the incidence of both frailty and HF increase with age,[24,78] frailty in advanced HF is not strongly associated with age[2] and may occur in very young patients, (3) frailty is more prevalent in women with HF compared with men, although the reasons are unclear,[79,80] (4) frail HF patients are more likely to have cognitive impairment,[15,81] and (5) frailty is more common in those with advanced HF symptoms,[82] but the relationship between frailty and New York Heart Association functional class is not always linear.[2]

The Frailty Phenotype Criteria and the Frailty Index have been the mostly widely used in HF,[2,41] albeit with modifications. For example, the Frailty Phenotype Criteria have been modified to address the problem of fluctuating fluid status in HF when assessing the unintentional weight loss criterion. Alternatives have been proposed, including changes in appetite[83] or assessment of lean muscle mass.[84] In advanced HF, the work by Jha et al has advanced the field the most in terms of validating frailty assessments, especially in those receiving LVAD and OHT, utilizing the modified Frailty Phenotype Criteria.[85,86] The Frailty Index has shown utility in identifying frail vs nonfrail among the general HF populations, ascertaining prognosis of frailty in HF, and assessing treatment effects from pre-existing data sets in electronic medical records[87] or large clinical trials.[88,89] However, a number of critiques[22,90] have limited its uptake in clinical practice, including the variability of multidomain data included across indices (e.g., comorbidities, symptoms) that also overlap with HF, the time-consuming nature of collating the data, and the inability to detect meaningful changes when comorbidities comprise the frailty assessment. Moreover, this broad measure limits the ability to target interventions at the individual level, which is particularly important in advanced HF given the heterogeneity of patients. Of the available screening tools, the Clinical Frailty Scale has been used in advanced HF studies[91] and shows agreement with frailty assessment tools,[90] and the self-reported FRAIL scale has also been used in HF,[92] but neither have been validated in the advanced HF population.

Proposed measurement tool of frailty in advanced heart failure

Our recommendations for a proposed measurement tool are outlined in Table 3. Our first recommendation is that a frailty assessment be performed in all patients with advanced HF, especially those undergoing LVAD implantation or OHT. We suggest a modified version of the Frailty Phenotype Criteria, which has been widely used and validated in the advanced HF population. We also suggest that all patients with advanced HF undergo additional assessments (e.g., cognitive function, depression). In Table 3, we outline suggestions for assessing each of the 5 frailty criteria (loss of muscle mass, weakness, slowness, physical exhaustion, and low physical activity) in clinical practice. We also outline options to consider for research purposes or further characterization. Given the considerable overlap of frailty with related concepts (further described below), considerations should be given to additional assessments that may elucidate the overall level of vulnerability in advanced HF (Figure 2).

While frailty screening tools are available (such as the Clinical Frailty Scale[93]), there is inadequate evidence to support a recommendation due to concern that screening tools may miss frailty among patients with advanced HF.[90] However, some studies have shown that gait speed alone is highly sensitive in identifying frailty among older hospitalized patients with decompensated HF.[94] The ideal screening test for frailty in advanced HF should be reproducible, valid, practical, and sensitive to change.[95] Lastly, if clinicians or researchers are interested in screening large datasets or the electronic medical record to quantify frailty, especially retrospectively, we recommend using the Frailty Index.[96]

Table 3 Suggested Approach for Frailty Assessments in Advanced Heart Failure.

Assessment approach			
Physical frailty: modified Frailty Phenotype Criteria			
	Tool	Scoring	Optional approaches[a]
• Loss of muscle mass/ unintentional weight loss	SHARE FI Scale: "What has your appetite been like?" Or "Have you been eating more, the same or less than usual?"	0 = The same or more than usual 1 = Less than usual	Quantification of muscle size using computed tomography scan of psoas muscle or pectoralis; arm circumference
• Weakness	5-repeat chair stands (i.e., rising up and down from a chair 5 times without using arms/hands)	0 = < 15 s 1 = > 15 s or unable to complete	Handgrip strength measured with a dynamometer
• Slowness	Gait speed test over 5 m	0 = ≤6 s (≥0.83 m/second) 1 = > 6 s (< 0.83 m/sec) or unable to complete	Gait speed test over 4-8 m
• Physical exhaustion	SHARE-FI Scale: "In the last week, did you feel on at least 3 days, that everything you did was an effort?"	0 = No 1 = Yes	Validated fatigue questionnaire (e.g., FACIT-Fatigue, PROMIS Fatigue)
• Low physical activity	SHARE-FI Scale: "How often do you engage in activities that require a low or moderate level of energy such as gardening, cleaning the car, or doing a walk?"	0 = Once a week or more 1 = Less than once a week or hardly ever	Validated physical activity questionnaire that captures low to moderate intensity activities (e.g., CHAMPS, PASE) or Duke Activity Status Index
Total scoring: 0 criteria met = nonfrail; 1-2 criteria met = prefrail; 3+ criteria met = frail			
Additional assessments to consider			
Cognitive function			Montreal Cognitive Assessment, Mini-Cog, or similar
Depressive symptoms			Patient Health Questionnaire-2 or -9 or similar
Screening approach for large datasets or medical records			
Frailty Index			
This approach counts deficits in health (e.g., symptoms, signs, diseases, disabilities, or clinical markers) Expressed as a ratio of deficits (as binary variables) to the total number of deficits considered (e.g., 10 deficits/40 considered = 0.25) See Rockwood et al 2008 for complete information on how to create a Frailty Index			

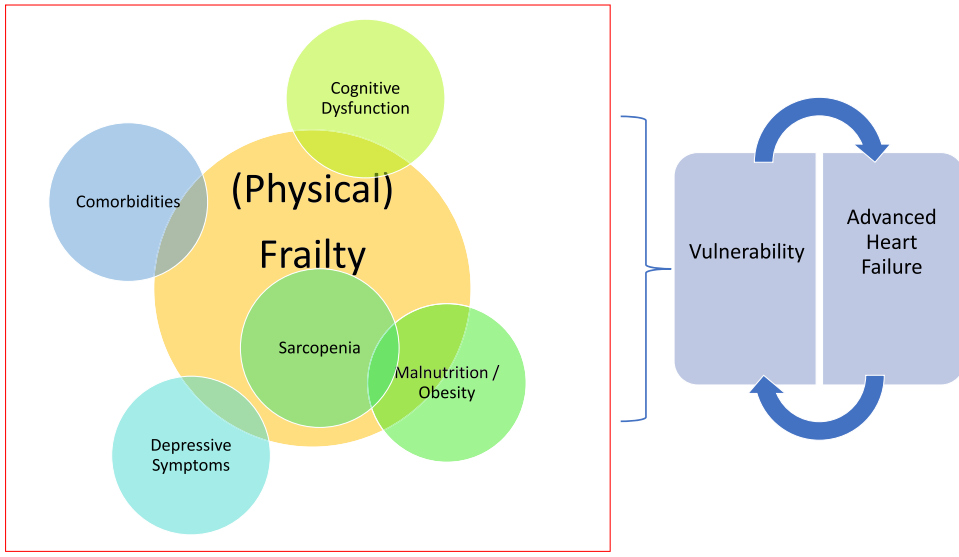
Abbreviations: CHAMPS, Community Healthy Activities Model Program for Seniors; FACIT, Functional Assessment in Chronic Illness Therapy; PASE, Physical Activity Scale for the Elderly; PROMIS, Patient-Reported Outcomes Measurement Information System; SHARE-FI, Survey of Health, Ageing, and Retirement in Europe-Frailty Instrument.

[a]Optional approaches for research (especially mechanistic), further investigating a particular criterion, or if patient unable to perform/ report.

When and how often to assess frailty

The optimal timing of frailty assessment in patients with advanced HF remains uncertain[83] as there are numerous factors to consider such as whether it is more appropriate to assess frailty while a person is hospitalized or in the clinic or community setting. It may seem logical and opportune to assess for frailty when a patient is in hospital, yet this may not be the most appropriate setting. A study of hospitalized patients with decompensated HF (84.6% with frailty or prefrailty) found that walking ability worsened during hospitalization in 27.5% and 21.8% of frail and prefrail patients, respectively.[97] Furthermore, objective physical measures may be impractical to measure with intravenous pharmacological and/or mechanical therapies.[24] Self-report questions could serve as an alternative option when unable to complete objective tests. Currently, it is unclear how often to reassess frailty. For routine clinic visits, frailty may not need to be reassessed frequently as studies of older adults have shown that patients remain in the same frailty category for years.[98] For patients who have been hospitalized or undergone surgical interventions, reassessing frailty within 3 to 6 months is likely informative to establish the new baseline and to track reversibility or persistence of frailty.[16,38,60] Defining the optimal timing of frailty assessments in advanced HF is a high priority for future research.

Figure 2 Relationship between the different domains of frailty and related concepts. Most studies of frailty in advanced HF focus on the physical aspects of frailty such as handgrip strength, gait speed, physical exhaustion (named "(Physical) Frailty" in the figure); however, other studies include related concepts such as "Cognitive Dysfunction," "Malnutrition/Obesity," "Sarcopenia," "Depression," and "Comorbidities" under the broader umbrella of frailty. For example, the Fried Frailty Phenotype Criteria include physical performance measures and sometimes including sarcopenia measures. Cognitive frailty would include physical frailty plus cognitive dysfunction assessments. The Deficit Index could include all of these domains or selected ones.



RELATED CONCEPTS OF FRAILTY IN ADVANCED HEART FAILURE

There is an important role of related concepts (e.g., sarcopenia) and domains (e.g., cognitive, psychological) when defining and assessing frailty (Figure 2). It is unclear where to draw the conceptual line around frailty: does it only include physical performance or do we add in closely related domains? Furthermore, due to the common co-occurrence of frailty with various comorbidities in HF, it can be difficult to disentangle one from the other, but they can be multiplicative in predicting adverse outcomes.[85] Based on the evidence to date, we suggest an assessment of the physical aspects of frailty as a starting point with suggestions to add additional domains.[76] Below we briefly describe these additional concepts, providing distinctions for conceptual and definitional clarity.

Sarcopenia and cachexia

Frailty is often linked with sarcopenia and cachexia. Sarcopenia is a characteristic feature of aging defined as a progressive loss of muscle mass and function.[99] The prevalence of sarcopenia is 20% higher in HF patients than in non-HF healthy patients of similar age and is even higher in younger patients with dilated cardiomyopathy.[100,101] Sarcopenic patients with HF have lower peak oxygen consumption, worse 6-minute walk test performance, and worse quality of life scores compared to their nonsarcopenic counterparts.[102] There are a variety of ways to assess sarcopenia, some of which overlap with frailty, such as low muscle mass, slowness, and weakness.[99] The unintentional weight loss question[24] and the 5-item SARC-F (strength, assistance with walking, rising from a chair, climbing stairs, and falls) questionnaire[103] are 2 self-report measures. Objective tools used to assess sarcopenia include dual energy X-ray absorptiometry,[101] bioelectrical impedance analysis,[91] and computed tomography-based measures.[91] In the advanced HF population, both pre-LVAD psoas[104] and pectoralis muscle[105] mass via computed tomography are sarcopenic markers that are significantly associated with adverse outcomes after LVAD implant.

Cachexia is defined as an unintentional loss of > 5% of total body weight over 12 months or less or body mass index < 20 kg/m^2[106] and is similar to the unintentional weight loss criterion of the Frailty Phenotype Criteria.[24] Cachexia frequently coexists with right ventricular dysfunction in advanced HF patients and, when present together, are associated with worse outcomes.[107] Sarcopenia and/or cachexia may serve as objective markers

that herald the onset of both advanced HF and frailty.[20] In the original Frailty Phenotype Criteria, unintentional weight loss was used as a proxy for loss of muscle mass; however, weight loss is an unreliable measure of loss of muscle mass in HF when fluid shifts (and thus weight shifts) are commonplace. In sum, sarcopenia and cachexia can be considered an element of frailty (including assessments), but they are not conceptually interchangeable with frailty.

Obesity

The relationship between obesity, advanced HF, and frailty is complex. Overweight or class I obesity status may have protective effects on outcomes in all patients with HF as part of the so-called "obesity paradox."[108,109] Obesity, however, may disguise frailty during the "eyeball assessment" of individuals. In fact, obesity has been linked with frailty,[110] and frail patients with HF have higher body mass indices, higher fat mass, and lower lean muscle mass compared with their nonfrail counterparts.[80] Sarcopenic obesity is a term used to describe high adiposity coupled with low muscle mass that is associated with exercise intolerance, increased rate of hospitalizations, reduced quality of life and mortality in HF.[111] Prognosis may be even more ominous for obese cachectic chronic HF patients compared to nonobese cachectic HF patients.[112] In sum, obesity in a patient with advanced HF should not obfuscate an assessment of frailty, and in fact, obesity likely potentiates frailty in advanced HF.

Multimorbidity

Multimorbidity is defined as the coexistence of 2 or more chronic conditions in the same individual.[113] Noncardiovascular comorbidities are common in patients with advanced HF, as ~80% of patients with HF have ≥4 noncardiovascular comorbidities.[114] Across studies, comorbidities (total number and specific types) have been strongly linked with frailty in HF.[80,115,116] However, the count of comorbidities (multimorbidity) should be distinguished from the resultant effect of multimorbidity on physiological systems (frailty). Comorbidity is considered an aggregation of diseases in an individual and frailty as an aggregation of loss of reserve across multiple physiological systems. Also there are individualized risk profiles associated with multimorbidity rather than the count of comorbidities, particularly for diabetes[117] (i.e., levels of complication should inform clinical management[118]), malnutrition,[119–121] and atrial fibrillation.[122–124]

Cognitive dysfunction

Cognitive dysfunction is highly prevalent in patients with HF, clinically under-recognized, and associated with poor health outcomes.[15,81,125] Patients with cognitive dysfunction have difficulties in HF self-care including adopting a healthy lifestyle, self-monitoring, and adherence to complex medication regimens.[126] Several tools are available for cognitive function assessment in HF patients, including the Mini-Cog[116] and the Montreal Cognitive Assessment.[8,85] The addition of cognitive impairment to frailty assessment has been shown to enhance the overall risk assessment provided by standard frailty measures in both hospitalized HF[116] and advanced HF patients.[85,86] In a study of advanced HF patients referred for pretransplant evaluation who underwent both frailty (modified Frailty Phenotype Criteria) and cognitive function (Montreal Cognitive Assessment) assessments, additional patients were identified using the cognitive tool with a similarly worse prognosis to the physically frail patients compared with those who were nonfrail on either measure.[86] Importantly, 12-month survival following LVAD or heart transplantation was lower in the cognitively frail than the nonfrail (56 ± 9% vs 85 ± 5%).[85] In sum, cognitive dysfunction often parallels frailty and offers additional prognostic information. We recommend that cognitive impairment be assessed as an additional domain to frailty.

Depression

Depression is a common comorbidity among all adults with HF and becomes increasingly prevalent as HF worsens.[127] Determining the presence of depression in advanced HF is relevant to all stages of the pre-, peri-, and post-LVAD or OHT course. Depression was also assessed alongside cognitive and frailty in the study by Jha

et al using the Depression in Medical Illness-10 questionnaire,[85] but it did not strengthen the relationship between frailty and mortality after advanced surgical therapies. However, the presence of depression in patients with HF undergoing advanced therapies is likely to have a greater impact on patient-centered outcomes such as quality of life and physical functioning. Larger prospective studies evaluating the prevalence of depression, and its prognostic value in addition to cognitive dysfunction and frailty are needed.

IMPLICATIONS AND MANAGEMENT OF FRAILTY IN PATIENTS WITH ADVANCED HEART FAILURE

Frailty may worsen symptoms,[6,7] impair self-care,[128] and lead to poorer outcomes in patients with advanced HF[129]; thus, early detection and implementation of intervention strategies to stabilize or improve frailty are essential in guiding management and improving outcomes.

Frailty in the advanced intervention population

Since patients being considered for advanced therapies such as LVAD and OHT have a high prevalence of frailty,[2,3,8,67,130–132] and frailty provides independent prognostic information[8,67,87,132–135] beyond current cardiovascular assessments, routine assessment for frailty is strongly recommended. Indeed, the ISHLT guidelines recommend consideration of frailty as a factor in determining candidacy for heart transplantation.[14] Despite the strong rationale for performing frailty assessments in these populations, frailty assessments are underutilized.[136] The lack of implementation of frailty assessments in clinical practice points to multifactorial translational barriers, including competing pressures for staff time, perception that assessment is time-consuming, lack of a standardized approach to assessment that is endorsed by cardiovascular societies,[15] and lack of understanding in how to apply findings from a frailty assessment. Available data suggest that routine and systemic assessment is associated with improvements in patient selection for advanced therapies and in length of ICU and total hospital stay, duration of intubation, care delivery, patient satisfaction and potentially outcomes.[8,10,11,15,43,87,119,136]

Left ventricular assist device implantation and orthotopic heart transplantation

Frailty assessments ideally would be performed in all patients with advanced HF being considered for LVAD or OHT both prior to and serially after the surgical procedure, but the optimal timing for frailty assessments is uncertain. Current practice is to assess frailty near the planned LVAD implantation, typically within a few weeks of a planned procedure. Similar recommendations are made for patients being considered for heart transplant, but since the timing of OHT is unpredictable, serial assessments while on the wait list are appropriate, especially if there is a change in the clinical condition. Serial assessments may also identify unsuspected or worsening frailty.

We recommend that the preimplantation assessment be as comprehensive as possible, including measures of frailty, as well as cognitive function and depressive symptoms (among others) based on data showing the additive predictive value of cognitive dysfunction in addition to frailty.[85,130] Concerns regarding the needed resources and time dedicated to such measurements appear to be overemphasized as most comprehensive assessments of frailty can be performed in under 30 minutes, and the benefit that they yield would outweigh the cost. However, recognizing time and training challenges for staff, it would be reasonable to focus on frailty assessments (outlined in Table 3) first and then assess or screen for related domains as needed (cognitive and affective). Assessments may be performed by any of the trained multidisciplinary staff (e.g., nurses, LVAD coordinators, heart failure specialists, physical or occupational therapists).

Postimplantation assessments would ideally include all domains assessed prior to LVAD placement or OHT. Given that frailty changes slowly post-LVAD [8,60] and could take up to 12 months or longer to see peak improvements, repeat evaluations are not recommended prior to 3 months in the absence of clinical indications but should be performed at 6 to 12 month intervals post-LVAD depending on available resources. For patients undergoing heart transplantation, improvements in frailty may be seen sooner than in patients undergoing LVAD placement, but recovery is highly dependent on presurgical condition and any clinical complications postoperatively.

Currently, most reports of frailty assessments prior to LVAD are performed in the inpatient setting. However, with 5-year survival rates improving,[137] a growing number of patients considering LVAD therapy is expected. As competing demands for time and urgency of surgical intervention decrease, this will likely facilitate time and resources for frailty assessments. However, the question of how to best assess frailty in patients who are critically ill on temporary mechanical support or unable to ambulate remains unanswered. In such clinical scenarios, approaches have included imputing low or zero scores for domains unable to be assessed (e.g., gait speed, chair stands, balance), restricting assessments to domains that can be reliably and accurately assessed despite mobility limitations (e.g., handgrip strength), or using computed tomography imaging of skeletal muscle such as the psoas, intercostals or pectoralis major muscles as a surrogate for frailty.[84,104,138,139] In Table 3, we provide a few options for each of the frailty criteria in these situations.

Reversibility postsurgical intervention

Frailty is potentially modifiable, providing further support that serial assessment is essential for providing optimal care. While there are only a handful of studies that have looked at reversibility pre and postsurgical intervention (LVAD implantation or OHT),[16,38,60] they describe several important findings. Despite the high mortality associated with frailty preprocedure, frailty did indeed improve immediately postintervention in some patients with most improvements seen > 3 months postprocedure. However, not all frail patients improved, and it remains unclear which baseline factors predict improvement in frailty following such interventions, although it is suspected that those younger patients with fewer comorbidities and age-related declines are most likely to have reversible frailty. Indeed, among those undergoing destination LVAD therapy,[60] the least reversibility was identified among those frail preintervention in the oldest cohort.

Frailty and nonsurgical interventions

Other interventions to manage frailty in patients with advanced HF focus on exercise and nutrition and require an individualized approach to management. These interventions may apply to either those undergoing advanced surgical interventions or not.

Exercise interventions

Typically, exercise interventions targeting frailty focus on mobility, balance, strength, and endurance training, whereas exercise programs or cardiac rehabilitation programs largely focus on aerobic activities.[140] One multicenter, randomized clinical trial, the Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) study, tested a targeted physical rehabilitation among 349 patients hospitalized for HF who had a high prevalence of frailty (97% assessed as frail or prefrail at baseline).[17] The study intervention was a novel physical rehabilitation program tailored to individual patients' deficits in multiple domains (balance, mobility, functional strength and endurance) and continually progressed for 12 weeks following hospital discharge.[17] Results in a diverse population of older adults with severe physical dysfunction and multimorbidity showed significant, clinically meaningful improvements in physical function and quality of life compared to usual care, which included access to usual care rehabilitation services.[17] The intervention was also associated with a significant improvement in frailty based on the Frailty Phenotype Criteria. Moreover, patients with worse baseline frailty had a more than 2.5-fold greater improvement in physical function in response to the study intervention compared to those who were prefrail, demonstrating that even very frail patients can respond well to robust physical rehabilitation.[141]

In addition to the encouraging results of the REHAB-HF study, there is a growing body of evidence indicating the beneficial effects of exercise in the general population of frail older adults, including improved frailty status, cognition, depression, cardiopulmonary and musculoskeletal dysfunction, and decreased falls.[17,142] According to a review of therapeutic interventions for frail older adults,[143] exercise training interventions were effective in improving performance on physical function tests. However, improvement was not sustained after completion of the intervention. Home-based exercises were effective and minimized regression when continued at the conclusion of supervised exercise training.[143] Additionally, moderate-intensity programs achieved greater results for muscle mass and function compared with low-intensity programs.[143] However, such moderate-intensity programs may not be feasible/safe for frail patients with HF who have significant impairments in multiple functional domains (e.g., balance, strength, and mobility).

Other studies have focused on resistance training as an intervention to promote increased skeletal muscle mass, muscular strength and endurance.[144] Resistance training also improves coordination[145] and vascular function,[146] and collectively contributes to improved functional capacity.[147] Increased strength that results from resistance training is associated with improved 6-minute walk test distance, sit-to-stand test, and balance.[148] Such interventions may be simplistic such as the use of exercise bands incorporated into home-based programs.[129] In frail older adults, exercise of about 45 to 60 minutes 3 times a week has shown positive effects on functional performance, walking speed, sit-to-stand test, stair climbing and balance, as well as depression and fear of falling.[149,150] Therefore, individualized, targeted exercise training or physical rehabilitation programs that first address deficits in balance, mobility, and strength prior to endurance training are promising strategies for management of frail patients with HF.

Nutritional interventions

Nutritional interventions could also be included in the management of frail patients with HF. Limited nutritional intake in patients with HF due to early satiety, chronic dyspnea, comorbid conditions, or dietary restrictions may increase the risk for nutritional deficiency.[67] In turn, nutritional deficits contribute to weight loss, frailty, and eventually cachexia.[67] According to a recent meta-analysis, dietary supplements of multinutrients and protein supplements were associated with improved physical functioning.[151,152] Vitamin D supplementation may also benefit frail patients with HF since vitamin D deficiency is very common in those with HF and can contribute to cachexia.[142] Although the effect of vitamin D supplementation on HF outcomes remains equivocal,[153,154] vitamin D supplementation has shown a modest beneficial effect on physical performance in frail individuals.[155] In a multicenter, randomized, controlled trial,[156] a 6-month nutritional support program that consisted of individualized nutritional counseling compared to usual care, the intervention was associated with lower 1-year mortality and HF readmission rates among malnourished patients with HF.[152] These results highlight the importance of nutritional counseling within the limitations of dietary adherence to multiple diets (e.g., low-salt, low-fat, low-cholesterol, diabetic diet, etc.) in those at risk for frailty.

Consideration of frailty and prehabilitation around procedures

Patients with HF often undergo complex procedures or surgeries as part of the management and treatment of HF as well as related cardiovascular conditions. Even in the very old, technological innovations enable us to treat these exacerbating cardiovascular conditions with minimally invasive, nonsurgical interventions such as percutaneous coronary intervention, transcatheter valve replacement or repair, cardiac resynchronization therapy, and arrhythmia ablation. Before embarking on these interventions, an assessment of frailty is relevant to understand how the frail patient values the potential outcomes arising from various options and how likely it is that the patient's symptoms and quality of life would be improved.

Within the realm of frailty, sarcopenia particularly may contribute to symptoms of fatigue, decreased exercise tolerance, and weakness, especially when muscle loss is severe or compounded by obesity (i.e., sarcopenic obesity), malnutrition, depression, or prolonged bedrest (i.e., posthospitalization syndrome). For older patients with HF, clinicians should address these factors, ideally within the context of a multidisciplinary geriatric team and geriatric principles[157] and possibly including a center- or home-based physical rehabilitation program initiated before (i.e., "prehab," if available) and continued after the intervention (i.e., rehab). For example, given an older HF patient with severe mitral regurgitation and severe frailty, an intervention to fix the heart valve, even if perfectly executed from a technical perspective, may not be sufficient to yield meaningful functional benefits without a parallel intervention to improve the patient's strength, mobility, and balance. The "technically successful failure" paradox has been reaffirmed in numerous studies showing high rates of midterm mortality, residual symptoms, worsening disability, and poor quality of life in 20% to 40% of patients with HF despite meticulous procedural execution; unaddressed frailty is often one of the primary predictors.[133,158–160] However, it remains underdetermined the degree to which frailty is reversible after these procedures.

To date there have been only 2 pilot studies that have assessed the role of prehabilitation programs in frail HF patients undergoing cardiac surgeries.[161,162] The first study[161] enrolled 11 patients listed for heart transplant into an 8-week prehabilitation program. While transplant-listed patients are considered too sick to participant in "prehabilitative" interventions, this study found 60% of patients improved in functional and exercise capacity, quality of life, and emotional wellbeing. In the second study,[162] 22 patients undergoing elective coronary artery

bypass grafting or valve surgery were enrolled into a 6-week home-based exercise program. These patients saw improvements in frailty (assessed using the Clinical Frailty Scale), short physical performance battery, and 6-minute walk test prior to surgery. The authors do note that a more sensitive frailty tool than the Clinical Frailty Scale may be required to identify impacts on patient's length of stay postintervention, and it was uncertain whether these were advanced stage HF patients. While both studies were small pilot trials, they highlight the role early detection of frailty may have in successfully implementing prehabilitation programs to prevent, or even reverse, physical and psychosocial deterioration prior to surgical procedures.

Incorporating frailty assessments into palliative care and self-care

Palliative care is an approach that improves the quality of life of patients and families through the prevention and relief of suffering, focusing on expert assessment and management of symptoms, evaluation and support of informal caregivers, and the interdisciplinary coordination of continuing care.[163] An assessment of frailty during the HF trajectory might help clinicians in their discussions of palliative care with patients and families and jointly decide on treatment options. Clinicians often have to revisit earlier decisions on therapy with their patients, recalibrating goals of care to ensure treatment policies remain appropriate. In the case of progressive frailty and/or progressive HF, previously expected outcomes may have become unrealistic and now represent false hopes.[164] There is little evidence on how to incorporate frailty assessments into palliative care and end-of-life care, although it is likely that frailty assessments could augment this type of care.[92] Moreover, given the high symptom burden that frail patients with HF experience, palliative care might provide the needed treatment to mitigate symptoms when other interventions are not possible or not working.[92]

Self-care is the cornerstone of management of patients with HF across the illness trajectory.[165] Self-care includes the need to practice behaviors that maintain physiological stability (e.g., adherence to medication, dietary and exercise regimens), recognize and interpret symptoms (i.e., symptom perception), and respond to symptoms when they occur (i.e., self-care management).[166] Self-care that is sufficient to improve HF outcomes such as physical functioning and quality of life[167] involves all 3 processes: self-care maintenance, symptom monitoring, and self-care management. In patients with HF, frailty may impact the ability to perform requisite self-care, such as meal preparation and dressing self, and access to health care. However, only 1 study has examined the relationship between self-care and frailty in HF, and they found that "social frailty" (defined as living alone, missing company and support from other people) affected self-care but not physical frailty.[128] Despite the lack of evidence, frailty assessments could be incorporated into discussions regarding HF self-care. Health care providers assess patient's self-care vis-a-vis adherence to medication and dietary restrictions, symptom severity, and changes in physical functioning. Incorporating frailty assessments as part of understanding a patient's ability to perform self-care is an important next step. Results can be used to optimize self-care through, for example, optimizing exercise regimens or referral for supervised physical rehabilitation. Similarly, nutritional counseling regarding multinutrient and protein dietary supplementation may be incorporated into self-care education. Future studies should explore how frailty assessments augment existing evidence-based self-care interventions.

SUMMARY, IMPLEMENTATION, AND FUTURE RESEARCH

Frailty is extremely common in patients with advanced HF and predicts a worse prognosis. The 2 syndromes likely worsen each other through complex molecular and cellular mechanisms that are not fully understood, but may include neurohormonal activation, immunosenescence, inflammation, skeletal muscle dysfunction, and adipose tissue dysfunction. While there is a general understanding on the concept of frailty in advanced HF, reaching consensus on an operational definition and an assessment of frailty has been challenging. Because of these challenges, many clinical practices have not implemented frailty assessments among patients with advanced HF. In this consensus statement, we have suggested an operational definition and assessment tool based on the evidence to date as well as the collective experience of experts in this field. Our goal with this statement is to provide a foundation from which to implement frailty assessments in clinical practice among all patients with advanced HF, especially those undergoing work-up for LVAD or OHT, and to standardize frailty assessments across research in advanced HF. Performing frailty assessments is absolutely necessary in patients with advanced HF in order to optimally plan therapeutic interventions targeted to

prevent the adverse sequelae in this population. Since this is a starting point, we also recognize that there are many facets in clinical care that need to be addressed to make this a reality as well as future research to address unmet needs and questions (Figure 3).

Implementation

Recognizing that there is a significant gap between recommending a frailty assessment in patients with advanced HF and routinely conducting frailty assessments in clinical practice, we have several broad recommendations that might facilitate successful implementation. First, it is important to identify the "who" and the "where" for frailty assessments. Different institutions have different workflows and defined roles, and it is recommended that each institution establish a reliable and consistent workflow to perform frailty assessments. It is important to recognize that anyone within the advanced HF team can perform a frailty assessment with training: physicians, nurse practitioners, nurses, nutritionists, physical therapists, among many others. Regardless of who is tasked with performing these assessments, we suggest identifying 1 or preferably 2 people who are able to perform these consistently.

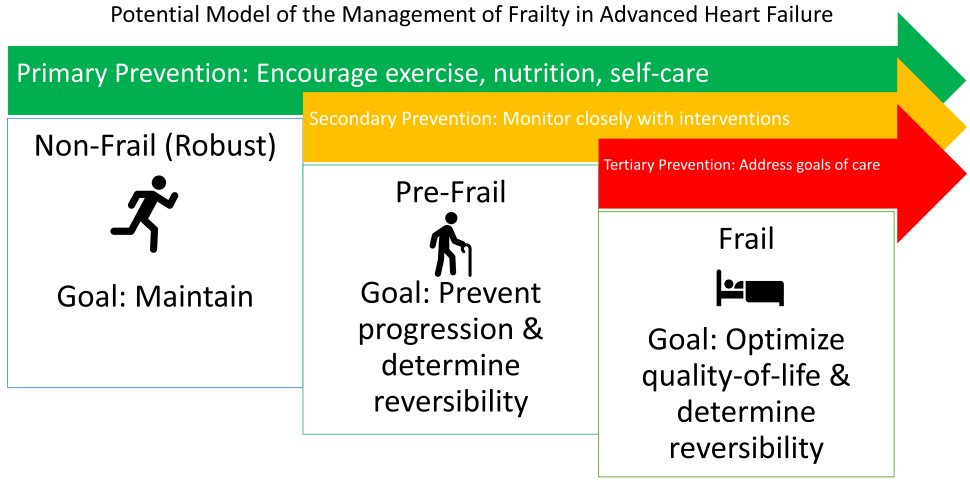
Second, we strongly recommend that frailty assessment prior to LVAD implantation or OHT become a requirement. Creating a procedure code (e.g., Current Procedural Terminology code in the US health care system) could provide a mechanism to reimburse for measurement of frailty and could provide needed resources for staff effort and time in this arena. Moreover, third party payers may mandate a frailty assessment before LVAD implantation or OHT. Additionally, professional societies could more formally endorse frailty assessments.

Future research

While our understanding of frailty in advanced HF has grown considerably, there are key areas that still need to be addressed. First, we need multisite studies to further test the reliability and predictive validity (including both clinical and patient-reported outcomes) of the recommended assessments. It is also important to assess the feasibility and practicality of assessing frailty in clinical settings. We will need to invest in the "how-to" implementation in real-world settings, perhaps utilizing implementation science principles.[168]

Second, we need to ensure that frailty assessments adequately capture change in frailty status, which in turn will determine the frequency and timing of assessments, especially after procedures. Additionally, understanding trajectories of frailty before and after interventions, especially LVAD and OHT, will help us to determine timing and

Figure 3 Potential overall model of the management of frailty in advanced heart failure. Ultimately, we hope further studies will demonstrate how to maintain nonfrailty (robustness) in advanced HF patients, how to prevent progression to frailty, and how to reverse frailty.



aggressiveness of specific interventions. This will help us to determine the "when" and "for whom" these interventions will have the most benefit.

Third, future studies need to examine and develop interventions that target the overall phenotype of frailty in advanced HF. Whether nutritional or exercise or multimodal-focused, interventions should consider the multifaceted nature of frailty. Additionally, recent research shows that guideline-directed medical therapy is often underutilized in frail patients with HF, possibly due to clinical biases[169]; but in fact, those who are frail may actually benefit the most compared with nonfrail counterparts.[89] The same has been shown for exercise studies.[88,141]

Fourth, future research should focus on how frailty assessments could augment palliative care strategies, including relieving significant symptom burden in advanced HF. Moreover, similar to how cognitive dysfunction affects self-care behaviors, frailty likely impacts the ability to perform adequate self-care. Future research should examine the degree to which frailty impacts the ability to perform self-care, and if targeting frailty might in turn improve overall self-care (or vice versa).

Finally, the concept of a resilience measure has been proposed in relation to frailty. Resilience is the individual's recovery potential and ability to restore to its current state (i.e., "bounce-back"). It may complement frailty and improve characterization of the differences in recovery potential between individuals with advanced HF.[15] In aging research, resilience was related to positive factors determining recovery such as strength, immunity, coping behavior, optimism, and good cognition.[170] Understanding the broader determinants of recovery may help provide a useful framework for coupling resilience and frailty, especially in the context of prehabilitation/rehabilitation.

Conclusion

Frailty assessments need to be performed in all patients with advanced HF. In this consensus statement, we reviewed the evidence to date and have put forth an operational definition and assessment tool to move this field forward. Future research will help us refine and implement frailty assessments so that frailty is routinely addressed across all centers.

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