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The Dual Burden of Frailty and Heart Failure

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ABSTRACT

Frailty is highly prevalent among patients with heart failure (HF) and independently predicts adverse outcomes. However, optimal frailty definitions, assessments, and management in HF remain unclear. Frailty is common in HF, affecting up to 80% of patients depending on population characteristics. Even pre-frailty doubles mortality risk versus robust patients. Frailty worsens HF prognosis through systemic inflammation, neurohormonal changes, sarcopenia, and micronutrient deficiency. Simple screening tools like gait speed and grip strength predict outcomes but lack HF-specificity. Comprehensive geriatric assessment is ideal but not always feasible. Exercise, nutrition, poly-pharmacy management, and multidisciplinary care models can help stablize frailty components and improve patient-centred outcomes. Frailty frequently coexists with and exacerbates HF. Routine frailty screening should guide supportive interventions to optimize physical, cognitive, and psychosocial health. Further research on HF-specific frailty assessment tools and interventions is warranted to reduce this dual burden.

Keywords: Heart failure; Rehabilitation; Frailty; Prognosis; Therapy

INTRODUCTION

Heart failure (HF) is a growing public health burden, affecting 1.5 to 3% of the adult population.[1] Alongside the cardiovascular symptoms, many patients with HF also exhibit frailty, a multisystem decline in physiologic reserve across clinical, physical, cognitive and social domains (**Figure 1**).[2] Frailty is highly prevalent in HF, affecting up to 80% of patients, and increases the risk of negative outcomes in patients with HF.[2,3]

Indeed, the presence of frailty worsens not only the clinical presentation of HF but also its prognosis and outcomes. Frailty independently predicts critical endpoints like mortality, hospitalization (longer hospital stay and hospital readmission), disability, non-adherence to guideline-based therapy and lower quality of life in patients with HF. This negative impact on outcomes translates into a greater utilization of healthcare resources.[3,4]

A recent analysis of over 3,400 HF patients from the Global Congestive Heart Failure registry demonstrated the value of assessing frailty for risk stratification. The registry included

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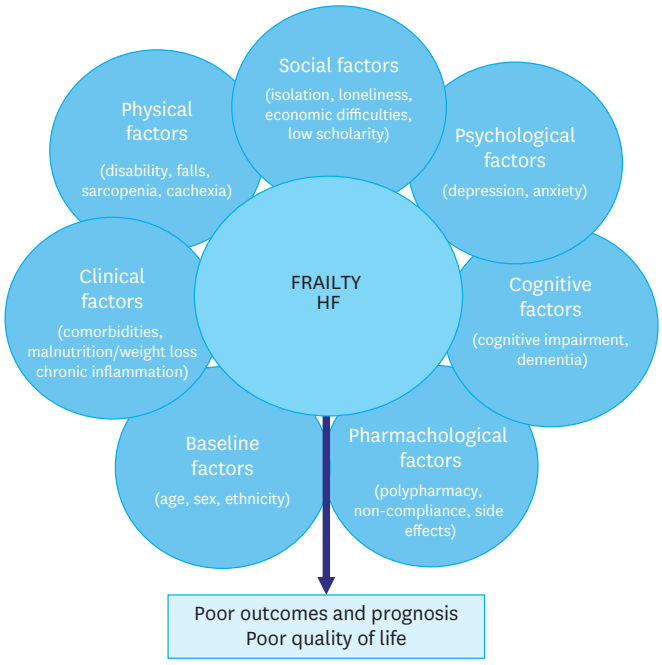

Figure 1. Factors influencing frailty in HF patients.
HF = heart failure.

patients from 40 countries across all income levels over 8 geographic regions. In this global cohort with mean age 61 years, frailty was evaluated using the Fried index criteria. Frailty provided additional prognostic information for mortality and HF hospitalization beyond the MAGGIC risk score alone.[5] This incremental benefit of frailty assessment held consistent regardless of country or income level, thus confirming the utility of frailty assessment for improving risk prediction in patients with HF.

Although the prevalence of both HF and frailty increases with aging in Western societies, frailty seems to be more strongly related to patients' vulnerability and their capacity to deal with stressors (biological age) than chronological age.[6] Therefore, frailty has been defined by the Heart Failure Association (HFA) of European Society of Cardiology as a "multidimensional dynamic state, independent of age, that makes the individual with HF more vulnerable to the effect of stressors."[2] The HFA, recognizing the key role of frailty in HF patients, suggested that healthcare professionals should 'monitor frailty and seek and address reversible causes (cardiovascular and non-cardiovascular) of deterioration in frailty score in elderly patients and it is in the process to develop a HF-specific tool to assess frailty based on four major domains, clinical, psycho-cognitive, functional, and social to be of use for all patients with HF independently of their chronological age.[2,7]

Indeed, given its heavy burden, detecting frailty in patients with HF is of outmost importance to effectively stratify risk and provide guidance for the management of frail HF patients.

EPIDEMIOLOGY AND IMPACT OF FRAILTY IN HF

Frailty affects almost one in every two adults with HF. Patients with HF are up to six times more likely to be frail, and frail individuals have a significantly higher risk of developing HF.

The reported prevalence of frailty among HF patients varies extensively, ranging from 15 to 80%, with the wide variability depending upon the severity of HF, the definition of frailty (physical vs multidimensional frailty), assessment methods used, and population characteristics (ethnicity, age, sex, comorbidities, etc.).[2,3,8]

As for ethnicity, Western and Asian HF patients differ for other components of frailty, such as physical features (e.g., body mass index or lean muscle mass).[9]

Specific data in Asian patients are scarce and affected by frailty assessment tools not validated for this population. Also, although Asian populations are often grouped together in clinical trials, there is a huge heterogeneity in the Asian population itself, comprising diverse ethnicities with differences in genetics and environmental and social factors. This has been demonstrated by the multinational Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry,[10] including 3,881 participants (age 61±13 years, 27% female), that showed specific ethnic (i.e., Malay) and regional (i.e., Southeast Asia) predisposition to frailty.

The data collected in the ASIAN-HF registry showed that Malay patients had the highest prevalence of frailty (83.8%), followed by Chinese (68.3%) and Japanese or Korean patients (67.2%),[10] Of note, most Asian patients with HF in the registry were frail despite relatively young chronological age.

The prevalence of frailty seems higher in those patients with HF who have a higher biological age, a higher number of comorbidities, a more severe status of HF, a higher level of dependency and functional limitations, and in those who are hospitalized.[11,12]

The prevalence of HF increases from <1% in adults under 55 years to over 10% for those over 80 years,[13] therefore, given the aging demographics of Western societies, the burden of frailty in HF populations is projected to grow markedly.

However, aging or, more specifically, chronological aging, is not

"per se" synonym of frailty as not all elderly patients with HF are inevitably frail. Indeed, biological age has a greater impact than chronological age on the prevalence, clinical presentation and outcomes of frailty. This suggests that all patients with HF, regardless of their chronological age, should be routinely evaluated for the presence of frailty as well as for the risk to become frail in HF clinics and wards.[2,6]

Several data suggest a higher prevalence of frailty in patients diagnosed with HF with preserved ejection fraction (HFpEF) compared to those with reduced ejection fraction (HFrEF). This association may be attributed to the increased presence of both cardiac and non-cardiac co-morbidities commonly experienced by patients with HFpEF. The burden of multimorbidity in HF negatively interfere with the-pathophysiologic mechanisms of frailty and HF thus increasing the risk of HF patients to be also frail. However, also patients with HFrEF have a high prevalence of frailty and in the PARADIGM-HF, ATMOSPHERE, and DAPA-HF trials up to 63% of the patients enrolled in these studies have been identified as frail.[14-16]

The link between the New York Heart (NYHA) functional class and the prevalence of frailty remains uncertain, as some studies have reported a weak association while others a linear correlation.[5,17] Due to the impact of the severity of the NYHA class in limiting the functional capacity of HF patients or in determining exhaustion and fatigue, it is clear that the results of the studies can differ according to the method used to assess frailty.

Irrespective of the measurement used to diagnose frailty, consistent evidence demonstrates that frailty exerts a significant negative impact on HF prognosis and outcomes, independently of cardiac dysfunction severity. Frail HF patients experience over double the risk of death compared to non-frail counterparts after adjusting for age, gender, ejection fraction, and functional class.[18,19] Compared to the non-frail, frail patients with HF have a 48% higher risk of death and a 40% higher risk of HF hospitalization.[12] This predictive value of frailty has been observed among out-patients, in-patients hospitalized due to exacerbation of chronic HF, as well as among patients hospitalized for implantation of a ventricular assist device.

Frailty is common in patients with advanced HF and has a key role in influencing the prognosis in those undergoing orthotopic heart transplantation and left ventricular assist device (LVAD) implantation.[20] Beyond survival and hospitalization, frailty predicts accelerated functional and pshyco-cognitive decline, higher risk of falls, social isolation, worsened NYHA class progression, and has a linear relationship with decreased quality of life, reflecting the higher vulnerability of these patients. Also, psycho-social factors, such as depression, anxiety, cognitive impairment, and social isolation, are strongly associated with negative short-term outcomes after hospitalization for HF, as suggested by the OPERA-HF study.[21]

From a health systems perspective, frail HF patients utilize more resources through increased hospital lengths of stay, readmissions, and nursing home placements.[4] In advanced HF patients undergoing LVAD therapy, a meta-analysis of 13 studies involving 3,435 patients showed that the presence of frailty was associated with negative outcomes, such as significantly longer time to extubation, hospital length of stay, and long-term mortality.[22]

These collective data underscore frailty's substantial contributions to morbidity, mortality and costs independently additive to HF severity itself.

PATHOPHYSIOLOGY OF FRAILTY IN HF

Frailty is a state of increased vulnerability to endogenous and exogenous stressors. Proposed contributors include chronic inflammation, neuro-hormonal derangement, changes in muscle composition and sarcopenia, endocrine dysfunction, oxidative stress, mitochondrial dysfunction, and depleted stem cell reserves.[23,24]

Although the exact mechanisms of frailty have not been completely understood, frailty seems more plausibly caused by a complex network of interconnected cellular and physiological alterations rather than a single unifying mechanism.

In addition, in elderly HF patients, the accumulation of molecular, cellular and tissue damages that occur with the aging process contributes to the multisystem dysregulation and depletion of homeostatic reserves thus increasing the risk of frailty.[25]

In patients with HF, pathways underlying HF and general frailty overlap, but unique HF-specific mechanisms are also likely to facilitate frailty development in this population. Indeed, the chronic hypoperfusion in HF, leading to multisystemic structural and functional abnormalities and vulnerability, together with chronic inflammation and the neuro-hormonal impairment, can overlap and play an additive role in explaining the high prevalence of frailty in patients with HF.[2,23-26]

Chronic systemic inflammation is postulated as a central mechanism driving frailty and HF. Patients with HF exhibit elevated

inflammatory cytokines like interleukin (IL)-1, IL-6, tumor necrosis factor-α, and C-reactive protein. Increased cytokine production and the imbalance between those with pro and anti-inflammatory effects, may both directly impair myocardial function and stimulate muscle catabolism and proteolysis, contributing to sarcopenia and weight loss.[27,28] Immuno-senescence, or age-related immune dysfunction, further propagates inflammation in elderly HF patients.[25]

Altered neurohormonal mechanisms leading to downstream anabolic-catabolic uncoupling and resulting in muscle wasting contribute to and facilitate the development of frailty. Increased sympathetic tone and renin-angiotensin-aldosterone activation mediate HF compensatory mechanisms but prove maladaptive long-term.

Age-related endocrine changes intrinsically predispose towards frailty, which are likely compounded in HF. Testosterone deficiency may also play a role in frailty and is plausibly accelerated in men with HF by obesity, inflammation, and altered metabolism; testosterone replacement has been demonstrated to improve exercise capacity and muscle strength in male and female patients with HF.[29,30]

Vitamin D deficiency is prominent in HF and associated with frailty through effects on muscle, inflammation, and cardiovascular health. HF treatments like loop diuretics may also worsen vitamin D deficiency by increasing urinary excretion.[31] The reduction in vitamin D levels can contribute to an enhanced release of renin, thus accelerating the progression of cachexia. Vitamin D deficiency increases also bone fragility that in turn may favour fractures that are often the primer of a series of events that lead to the death of many frail patients.

A recent meta-analysis has shown that both hypovitaminosis D and androgen deficiency can have a role as markers of poor health status in patients with frailty.[32]

Deficiencies in key micronutrients and protein-calorie malnutrition frequently develops in HF and portends poor prognosis and frailty. Deficiency of other essential nutrients like selenium, zinc, and vitamin C is likewise correlated with frailty severity.[24,31] Causes of micronutrients deficiency include inadequate intake, impaired absorption, and hypermetabolism in HF.

The presence of chronic impaired cerebral perfusion (low flow HF), the autonomic dysregulation and the frequent presence of cardiovascular risk factors affecting cerebral perfusion play a fundamental role in the occurrence of declining cerebral function particularly in elderly frail patients with HF.[33]

Therefore, frailty in patients with HF presents multiple underlying pathophysiological mechanisms that often overlap increasing the vulnerability to stressors.

FRAILTY AND RELATED CHALLENGES IN ITS ASSESSMENT IN HF

According to the aforementioned HFA definition[2] this state of vulnerability includes: 1) the multidimensional characteristic of frailty encompassing the physical component, such as sarcopenia and functional impairment; 2) a dynamic nature, reflecting the possibility to have deterioration or improvement of frailty; 3) the potential to be revertible as some components are modifiable and treatable; 4) a link with aging but at the same time its independence from it.

Four main components—clinical, functional, psycho-cognitive and social—have been identified to define frailty in HF patients with some variables overlapping across the four main domains.

Frail individuals with HF may present disability, physical or mental, thus interfering with the patients' ability in performing essential tasks for independent living, self-care, and overall health (such as basic activities of daily living [ADL] or instrumental ADL [IADL]). However, although frail patients with HF, particularly the elderly, are at higher risk of developing disability, not all frail individuals have an impairment in their ADL and IADL.

Integrating concepts of impairment of physiological reserve across organ systems and aggregation of deficits of the 4 different main domains that deteriorate the patient's health status favoring frailty may yield a more comprehensive and reliable measure of HF-related frailty.

Optimal criteria for frailty and tools to correctly identify it in HF remain debated. Given its overlap with the clinical feature of HF and its prognostic significance, it is recommended to routinely assess frailty in HF clinics and wards. However, in busy clinical practices this can be possible only if a simple, not time-consuming and validated tool is available to be used by all healthcare professionals. To date, a myriad of tools exist to assess frailty but none of these have been specifically optimized to identify frailty in HF patients.

The available instruments used for assessing frailty can be divided into two main groups according to the two fundamental concepts of frailty: the physical frailty phenotype and the cumulative deficit model.[34,35]

The most used instruments assessing the physical components of frailty are the Physical Frailty Phenotype model, the short physical performance battery (SPPB), or other single item measures (i.e., five-metre gait speed, hand grip strength, etc.), while those using a multidimensional approach are the comprehensive geriatric assessment, the frailty index, the Edmonton Frailty Scale, the Clinical Frailty Scale (CFS).[36-38]

The comprehensive geriatric assessment represents the gold standard in geriatric patients to identify elderly frail patients but it is resource consuming and may not be sensitive enough to detect frailty in younger HF patients. Other multidimensional indices are less frequently utilized in clinical practice being considered time consuming.

The CFS is an attractive instrument to use in clinical practice due to its simplicity, lack of reliance on specific equipment (i.e. dynamometers) or assessment (i.e. questionnaire) beyond the patient's clinical evaluation. In addition, its ability to predict negative outcomes, such as mortality and institutionalization, contributes to its appeal. However, the CFS can be biased by the subjective evaluation of the healthcare professional performing the assessment or lumping together the information about cognition, mobility, function and co-morbidities based on the medical history and physical examination; in addition, the lack of recording the specific component/s impaired and involved in determining frailty can limit the ability to establish a tailored plan of treatment.

Although the instruments based on the physical frailty phenotype reliably predict outcomes, they fail to measure other determiners of frailty, such as the pshyco-cognitive and social components that can interfere with clinical aspect, outcomes and adherence to treatment, as well as to adequately distinguish contributions of HF itself versus frailty. The failure to assess the multidimensional components of frailty can underestimate the real prevalence of frailty in HF patients and limit the possibility to define a centered care-plan.

The role of the different components of frailty, and in particular of the physical, cognitive and social components, has been evaluated in the FRAGILE-HF study, a prospective multicenter cohort study enrolling consecutive hospitalized patients with HF aged ≥65 years.[39] This study demonstrates not only the coexistence and overlap of multiple frailty domains but also that those patients with a greater number of frailty domains have more symptoms, a greater clinical and functional impairment in different organs as well as higher rates of mortality and all-cause death/HF rehospitalization.

Current models to diagnose frailty have limitations in distinctly distinguish frailty from intrinsic HF symptoms due to their clinical and pathophysiological overlap, thus causing the risk to under or overestimate the real prevalence of frailty in HF patients. Components like slow gait and fatigue overlap with the decreased exercise tolerance and shortness of breath due to cardiac dysfunction in HF patients; weight loss should be discriminated as a consequence of the diuretic treatment or loss of muscle mass.

The lack of standardized criteria and the lack of adjustment of the currently used cut-offs in HF patients due to decreased exercise tolerance and shortness of breath related to the cardiac dysfunction also hinders reliability and clinical adoption.

Also, if the items included in the frailty score are related more to HF than frailty they may lead to an incorrect assessment of frailty because of the dynamic changes in the clinical manifestations of HF may translate in an incorrect assessment of frailty.

These limitations reveal the need for an instrument designed specifically to diagnose the multidimensional features of frailty in HF distinct from its primary pathophysiology.

POTENTIAL APPROACHES TO HF-SPECIFIC FRAILTY ASSESSMENT

An optimized frailty screening tool designed for HF patients should fulfill several key criteria.[18] It needs adequate sensitivity and specificity in accurately identifying frailty pathology separate from HF itself; should have prognostic accuracy for hard endpoints like mortality and hospitalization but also for patient-centered endpoint, such us quality of life; should be reliable and easy to use to enable routine adoption in busy clinics. Various approaches could be explored to develop and validate a precision frailty measure for HF patients.

Multidimensional models integrating phenotypic, physiological and psychosocial factors related to frailty, analyzed using machine learning computational approaches, could help parse apart HF versus co-existing conditions. This could delineate shared versus discrete pathways and enable precision interventions. Integrating patient-reported outcomes through a HF-focused frailty surveys may have an additional value in the assessment of frailty. Ultimately, a multifaceted tool incorporating clinical, functional, and patient-derived components may prove optimal.

Current frailty assessments demonstrate inadequate specificity for distinguishing frailty from inherent HF manifestations and

severity. An instrument optimized for and validated in the HF population would facilitate targeted risk stratification and enable therapies directed at frailty.

Developing such a tool poses challenges but offers the promise of precision medicine for this vulnerable group of patients. With HF prevalence increasing in our aging population, refining frailty measurement is imperative to reduce the burden of this deadly combination. A thoughtfully designed and scientifically rigorous approach to creating an HF-frailty index could facilitate risk stratification and guide management and provide enormous clinical value in caring for these complex patients.

To this end, a Delphi process involving different healthcare professionals in the field of both HF and frailty and the involvement of several scientific societies including the HFA, the Korean Society of Heart Failure and the Chinese Heart Failure Society is undergoing with the aim to develop an easy and clinically centered frailty score. The new score will soon enter the test phase to ascertain its diagnostic and prognostic value in clinical practice.

MANAGEMENT OF FRAILTY IN HF

Due its multidimensional nature, the management of frailty should be tailored and finalized to target all the modifiable and treatable components of the clinical, physical, social and cognitive domains in order to reverse, when possible, frailty. Indeed, up to a point of no return (pre-death), frailty is potentially reversible (**Table 1**). The potential reversibility of frailty highlights the importance of an early diagnosis of frailty in patients with HF in clinical practice. This is a key aspect, considering that post-hoc analyses of recent randomized controlled trials in both HFpEF and HfrEF have clearly shown that HF treatments, have not only beneficial effects in frail HF patients but that these benefits are greater in frailer patients.[40-42]

Management of HF and the clinical components

Although a wide range of concomitant clinical diseases characterize frail patients as well as HF patients, a disease-specific approach, finalized to precise prescriptions for each disease, should be avoided and a more comprehensive holistic approach effectively addressing the systemic effects and global risk associated with multimorbidity should be promoted in HF frail patients. In fact, the use of guideline-directed HF therapies, such as angiotensin-converting enzyme inhibitors, beta-blockers, and mineralocorticoid antagonists, although it could be challenging in frail patients with HF, especially if older, due to their increased vulnerability to the adverse effects of these medications, should be promoted due to their beneficial effects.[24] Both pharmacological and non-pharmacological treatments should be implemented and tailored on each patient with the aim to prioritize those treatment with a more meaningful effect in improving quality of life and reducing the occurrence of negative outcomes. Thus, treatment of frail HF patients requires a shift from the traditional model of disease-specific management

Table 1. Main targets for the management of frailty in heart failure

Therapy	Aim
Management of impaired clinical components and multimorbidity	· Avoid a disease-centered approach · Promote a patient-centered approach · Deprescribe to reduce adverse events
Management of impaired physical components	· Regular physical activity (resistance-based training, aerobic training, balance and coordination training, functional exercise, inspiratory muscle training; supervised and non) · Physical independence · Adequate protein intake
Management of impaired psychological and cognitive components	· Cognitive interventional approaches and support · Emotional interventional approaches and support · Adequate protein and vitamins intake
Management of social components	· Social support (group-based program/activities; community recreative programs) · Self-care
Nutrition	· Dental care · Dietary counselling · Weight monitoring · Adequate protein and vitamins intake · Iron supplementation
Quality of life	· Improve quality of life
Continuity of care	· Special pathways for frail patients · Digital health
Management of polypharmacy	· Medication review · Deprescription · Drug interaction assessment
Avoid frailtyism	· Promote an objective assessment of frailty vs eye-ball evaluation

to a systemic approach (e.g., exercise and physical rehabilitation, diet, nutritional support),[24] as described below.

To date, the weight and the clinical and prognostic impact of the single comorbidities, often aggregated in recurrent phenotypes are still not well known in frail HF patients. In addition, how clinicians should prioritize the different treatments in HF frail patients remains to be understood.

Although the best medical therapy for the treatment of HF should be promoted in all patients including those with frailty, it has been shown that frail HF patients are less likely to receive the needed HF medications. This is most probably linked to the fear that these patients have a higher risk of experiencing negative outcomes. Similarly to ageism (discrimination against people on the basis of their age), frailtyism is a stereotyping, prejudice, and discrimination against people on the basis of the presence of frailty. Frailtyism, often based only on an eyeball test, can preclude the adequate treatment of flail HF patients and the management of the reversible components of frailty.[43] For instance, advanced HF patients can be erroneously deprived of potentially high-risk but effective procedures such as LVAD. On the other hand, the safety of device therapy is questionable in frail HF patients due to the high risk of adverse outcomes in this population.[3] The use of a specific, reliable tool to assess frailty in HF is therefore needed to avoid the risks of an eyeball evaluation of frailty and preclude device therapy when necessary.

Exercise training

Physical exercise helps counter frailty and is strongly recommended for those frail HF patients able to participate.[44-46] Resistance and endurance exercise interventions have shown effectiveness in mitigating muscle loss and in enhancing physical capacity in HF patients.

A comprehensive rehabilitative regimen including aerobic, strength, and balance exercises could be an efficacious approach for enhancing mobility and gait, augment muscle mass and strength, reduce the occurrence of falls, optimize functional performance in daily activities, increase caloric expenditure and glucose metabolism, and support cardiovascular health.

Exercise can also have beneficial effects on mental disorders, such as depression and anxiety, and cognition and at the same time reduce isolation when included in the setting of a rehabilitation program.

Functional exercise training finalized to improve the possible impairment in performing basic ADL can also be of help in frail HF patients as well as inspiratory muscle training to improve exercise tolerance. Due to its ability to positively act in all the domains of frailty together with the beneficial effect on the overall quality of life and prognosis, when possible, regular exercise should be promoted as part of daily routine and considered as one of the crucial treatments of frail HF patients.

Exercise intensity should be personalized and tailored based on frailty severity and HF clinical status and revised periodically due to the clinical fluctuation of the two diseases. Although most patients with frailty and HF can safely perform exercise, in particular if with appropriate monitoring, a risk assessment including falls, hypotension, and arrhythmias warrant consideration.

In a post-hoc analysis of the HF-ACTION trial, aerobic exercise training in patients with chronic stable HFrEF was associated with a comparable improvement in QOL among frail and non-frail participants but a significant reduction in the risk of all-cause hospitalization was observed only among frail participants.[15] Similarly, but in the setting of acute HF, a prespecified secondary analysis of the REHAB-HF trial, showed that a tailored and multidomain physical rehabilitation intervention finalized to improve balance, strength, mobility, and endurance was able to improve the SPPB score and reduced all-cause hospitalization rate.[47] In this analysis a higher significant improvement in physical function was seen in patients with worse baseline frailty status compared to those who were prefrail.[8]

These data suggest the key role of physical rehabilitation and exercise in the management of frail HF patients, even though further studies are required to give clinicians indication on how to personalize the exercise routine in patients with HF and frailty.

Nutritional interventions

Nutritional deficits are common in patients with HF and frailty due to inappetence, taste changes, early satiety, altered gastrointestinal absorption, as well as depression or cognitive dysfunction. Additionally, HF-related dietary restrictions further contribute to the development of malnutrition and a low protein consumption in HF has shown to increase the level of congestion and the risk of mortality.[31,46,48]

Nutritional intervention should be comprehensive from dental care to dietary counselling and should aim both to promote an adequate and balanced intake of food as well as supplement the possible deficiency commonly found in HF patients with frailty. Nutritional and caloric supplementation are effective in the treatment of weight loss and protein supplementation increases muscle mass, thus having potential beneficial effect in frail HF patients.

Vitamin D repletion in those HF patients who are deficient improves strength and physical function and reduces the excessive aldosterone levels among HF patients, due to the negative regulator role of vitamin D on the hormone renin.[49,50]

Up to 70% of HF patients have iron deficiency with or without anemia, playing a negative role in determining negative outcomes.[51,52] A recent analysis of 6,406 participants aged 60 years or older followed for 13-years follow-up form NHANES 2007–2014 study showed that elderly HF patients with low levels of hemoglobin and frailty have the greatest risk for all-cause, cardiovascular, cancer, and non-cancer/non-cardiovascular mortality, compared to those without frailty. This preliminary data suggests a potential role of iron supplementation specifically targeted for the management of frailty in HF patients.[53]

A meta-analysis of seven randomized controlled trials showed, although with a low quality level of evidence, that the combination of exercise rehabilitation and nutritional interventions, including essential amino acids and proteins, may improve some muscle functions in patients with HF and frailty. However, to date clear indications on nutrition in frail HF patients are still lacking.

Polypharmacy management

Polypharmacy is highly prevalent in HF patients and contributes to side effects, poor adherence, risk of falls, and need for hospitalization. Reducing inappropriate medications is a crucial initial measure in enhancing prescribing practices, which may involve the cessation of medications that offer limited advantages and/or have the potential to have a detrimental effect. Rational discontinuation based on limited life expectancy, drug interactions, and adverse effects is important. Simplifying complex regimens and the use of fixed dose combination pills can help adherence and reduce the risk of side effects. Collaborative medication reviews balancing HF efficacy, frailty risks, and patient goals should guide deprescribing.

FUTURE DIRECTIONS

While several interventions are promising for the treatment of frailty, substantial research gaps remain in proven therapies for frail HF patients. Development and validation of HF-specific frailty assessments would enable targeted therapies.

Comparative effectiveness studies of exercise protocols, nutritional supplements, vitamin repletion, and polypharmacy management could illuminate optimal regimens. Telecare approaches leveraging mobile health technology present another opportunity. Patient-centered outcomes research would ensure alignment with patient priorities. Advancing proven, pragmatic interventions to mitigate frailty remains a critical need in HF care.

The main objectives of patient-centered care and multidimensional management of frailty in HF patients are to improve quality of life and to prevent the occurrence of negative outcomes, by maintaining and promoting functional independence, detecting and treating psychological impairment, avoiding loneliness and encouraging social contact and participation in social activities, avoiding unnecessary admissions to hospital or into long-term care facilities. In addition, key aspects in the management of frail HF patients are 1) to adopt a simple but robust tool for the detection of frailty, thus avoiding to use eyeball tests that can increased the risk of frailtyism; 2) to promote continuity of care through the involvement of a multidisciplinary team; 3) to adopt the opportunities of digital health to monitor and manage patients centralising the management of patients in the community rather than in the hospital.

CONCLUSION

In conclusion, frailty is highly prevalent among HF patients and its routine assessment using simple, validated tools is a key factor to promote a multidisciplinary, patient-centered approach addressing the potentially reversible components of frailty. Further research on HF-specific frailty interventions is warranted.

Since frailty in HF may be partially reversible or preventable, cardiac rehabilitation or prehabilitation as well as the holistic therapeutic approach may play an important role in modifying its burden in patients with HF. The treatment of frailty in HF should be multifaceted, aimed at its main components, and individualized in order to treat comorbidities.

The main challenges for an adequate management of frailty in HF are the translation or the daily assessment of frailty from the setting of research into an easy and practical clinical tool and a clear understanding on how to tailor the management strategies to effectively target the different domains of frailty.

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

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