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REVIEW

Comorbidities

Frailty and Heart Failure: Clinical Insights, Patient Outcomes and Future Directions

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Abstract

Frailty is common among heart failure (HF) patients and linked to increased risk of adverse outcomes. Contributing factors include inflammation, sarcopenia and neurohormonal issues which diminish physiological reserves and accelerate the decline of health. Managing frailty in HF requires a multidisciplinary approach to address physical, nutritional and pharmacological needs. Structured exercise and dietary support can improve physical function, while careful medication management, especially with polypharmacy, reduces frailty-related risks. Telemedicine and wearable tech facilitate continuous monitoring and timely intervention, especially for those in remote areas. Future research should develop standardised frailty assessment tools specific to HF, enhancing risk stratification and personalised care. Studies on underlying mechanisms, such as inflammation and mitochondrial dysfunction, could lead to new therapies. Addressing socioeconomic factors can also improve care equity. This review summarises the mechanisms, clinical characteristics and impact of frailty on HF, highlighting challenges in treatment and opportunities for improving patient outcomes.

Keywords

Frailty, heart failure, sarcopenia, telemedicine, inflammation, frailty syndrome

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Frailty is a complex syndrome characterised by reduced physiological reserve and increased vulnerability to falls, hospitalisation and mortality. It is commonly associated with advanced age, but can affect younger adults with chronic conditions or iatrogenic complications.[1] Unlike other medical conditions, frailty is not fully captured by measures of disease severity, yet is a critical predictor of poor health outcomes.[2] Heart failure (HF) affects approximately 64 million people globally, predominantly in ageing populations, with prevalence rising to 8.3% in individuals over 50 years old. Key symptoms include dyspnoea, fatigue and oedema, varying in severity with disease progression.[3,4]

Frailty often coexists with HF, affecting 30–60% of patients with reduced ejection fraction (HFrEF) and manifesting as limitations in physical and cognitive function.[5] Frailty's impact on HF outcomes is profound, with frail patients experiencing higher rates of hospitalisation and mortality. Gender disparities also exist, as women are more frequently frail, but frail men exhibit worse outcomes.[6] In regions with limited healthcare access, the co-occurrence of HF and frailty presents unique challenges, necessitating global strategies to address barriers in care delivery and improve outcomes.[7]

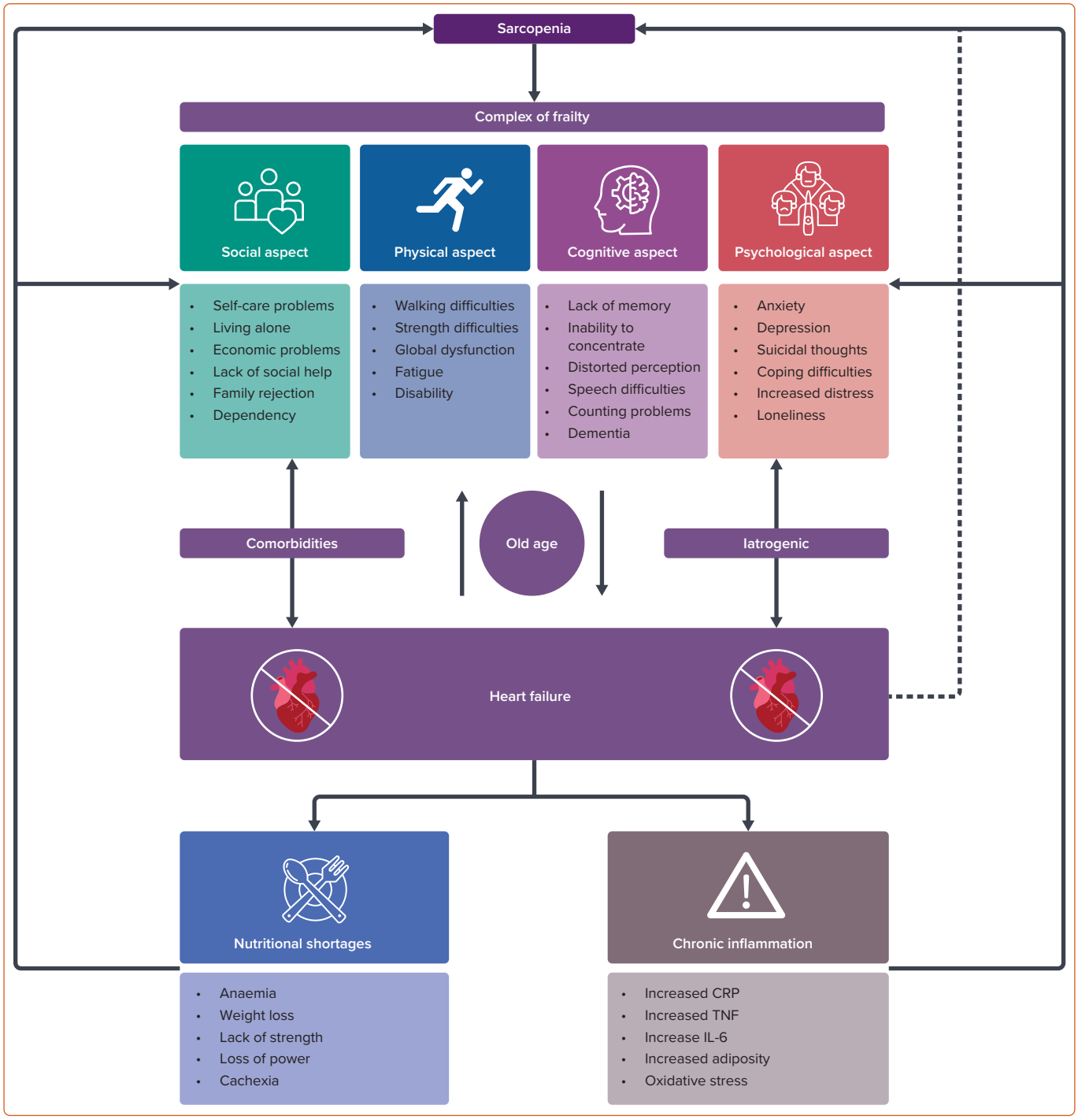
In this review, we summarise current knowledge about the mechanisms underlying frailty syndrome and its associations with HF. We highlight the clinical characteristics of frailty syndrome, its impact on HF treatment and challenges associated with frailty in HF patients. We further address current approaches to measuring and managing frailty in the HF population, based on available studies and recent insights.

Mechanisms of Frailty in Heart Failure

Frailty in HF is underpinned by complex mechanisms involving inflammation, oxidative stress and sarcopenia (muscle wasting). Chronic inflammation, characterised by elevated levels of markers such as C-reactive protein (CRP) and interleukin-6 (IL-6), accelerates the breakdown of muscle fibres and reduces the body's capacity for regeneration.[8] Mitochondrial dysfunction, seen in both HF and frailty, further diminishes energy production, leading to fatigue and reduced physical resilience.[9] Marked by impaired energy production and increased oxidative stress, mitochondrial dysfunction plays a pivotal role in frailty pathogenesis by exacerbating muscle wasting and cardiovascular decline.

Sarcopenia, defined as the loss of muscle mass and strength, is a key

Figure 1: Clinical Conditions Associated with Frailty



CRP = C-reactive protein; IL-6 = interleukin-6; TNF = tumour necrosis factor. Created using resources from Flaticon.com.

component of frailty syndrome and is particularly pronounced in patients with HF. It results from reduced blood flow and oxygen supply to tissues, contributing to diminished physical capacity, insulin resistance and inflammation. Changes observed in sarcopenia include weakened muscle fibres, a higher proportion of fast-twitch fibres and reduced oxygen usage efficiency in energy processes.[10,11]

Emerging evidence suggests that interactions between neurohormonal pathways and chronic inflammation play a critical role in accelerating the progression of frailty in HF patients. In particular, cytokines, such as tumour necrosis factor-α (TNF-α) and IL-6, which are upregulated in HF, have been shown to trigger muscle wasting and increase oxidative stress. These inflammatory markers are also linked to cognitive decline, further complicating the clinical management of frailty in elderly patients.[12] Cytokine dysregulation, particularly involving interleukin-1β and TNF-α, has been identified as a key driver of frailty in HF. This inflammatory response not only accelerates muscle wasting but also impairs cardiac function, increasing the overall disease burden in frail HF patients.[13]

Emerging research also suggests that gut microbiota may play a pivotal role in the development of frailty in HF patients. Dysbiosis, or an imbalance in gut bacteria, has been linked to increased systemic inflammation, which exacerbates both frailty and HF progression. Therapeutic approaches aimed at restoring healthy gut microbiota through probiotics

or dietary interventions are being investigated for their potential to mitigate frailty symptoms in HF patients.[14]

Additionally, neurohormonal dysregulation plays a key role in the onset of frailty in HF patients. Elevated levels of cortisol, driven by chronic stress, impair the body's ability to build muscle and respond to physical stressors.[15] The interplay between sarcopenia, inflammation and neurohormonal dysfunction exacerbates frailty, leading to a rapid decline in physical and cognitive function as well as increased mortality risk (*Figure 1*).[16]

Clinical Conditions Correlated with Frailty

While ageing is expected, some HF patients experience an unexpectedly rapid decline in their health, a state described as 'frailty'. The exact reasons behind accelerated ageing in HF are still under investigation, but scientists suspect several potential mechanisms are at play, including imbalances in the immune system and hormones, which lead to inflammation, cellular stress and an overactive nervous system. Additionally, cells may malfunction and age prematurely, leading to sarcopenia and overall wasting. All these processes are present in HF, but it seems that frailty somehow fuels their progression.[2] The high prevalence of frailty in chronic HF patients likely stems from multisystem dysfunction such as chronic inflammation, multiple coexisting health conditions, advanced age and persistent muscle deficits.[10]

Frailty is intricately connected with various comorbidities seen in HF patients, including diabetes, chronic kidney disease (CKD) and anaemia. These conditions further exacerbate the physiological decline seen in frailty, leading to worsened outcomes.[17] For example, diabetes accelerates muscle loss due to insulin resistance, while CKD contributes to malnutrition and reduced muscle function through the accumulation of toxins in the body. Studies have shown that CKD exacerbates frailty by increasing inflammation and contributing to muscle wasting. Moreover, CKD-related electrolyte imbalances and toxin buildup further impair physical and cognitive function in frail HF patients.[18] Chronic obstructive pulmonary disease is also a significant HF comorbidity, exacerbating frailty by impairing oxygen transport and reducing physical capacity.[19]

Furthermore, cognitive decline is often seen in frail HF patients. This may be related to reduced cerebral perfusion and increased inflammation and oxidative stress, which are common in both frailty and HF. Cognitive impairment makes it difficult for patients to adhere to treatment plans, leading to poorer health outcomes and higher mortality rates.[16] Additionally, depression and anxiety, both prevalent in HF patients, further exacerbate frailty by reducing motivation and energy levels needed for physical activity and self-care.[20] Addressing cognitive impairment in frail HF patients is critical for improving adherence to treatment regimens and overall quality of life.[21]

HF creates persistent low-grade inflammation due to excessive nervous system activity and elevated stress hormones. This inflammation leads to detrimental changes in muscle structure, decreasing both muscle mass and strength and ultimately contributing to physical frailty. Additionally, inflammation worsens organ damage from fluid buildup and oxygen deprivation, both common features of HF. The development of other chronic conditions, such as kidney disease, further erodes the body's physiological reserve and increases frailty.[5] As ageing and HF progress, several biological processes deteriorate, leading to the accumulation of DNA damage, impaired cellular waste removal and malfunctioning energy production. These changes can disrupt cellular metabolism, lead to cellular ageing and ultimately cause cell death. This triggers the body's natural defence system to overreact, releasing inflammatory molecules into the bloodstream.[22]

Adults with HF often exhibit elevated levels of inflammatory markers, such as CRP, tumour necrosis factor-α and IL-6. Studies have linked these elevated markers to an increased risk of developing HF in elderly patients.[23] IL-6, in particular, is more prevalent in older HF patients with additional cardiovascular conditions. Research suggests that higher IL-6 levels are associated with an increased risk of mortality in individuals with HF.[5]

People with HF are more likely to suffer from nutritional deficiencies and malnutrition, highlighting the importance of careful dietary planning. These nutritional issues can contribute to weight loss, a condition called cardiac cachexia and the overall weakening associated with frailty.[10] Dysregulated neurohormonal mechanisms, including impaired cortisol regulation and disruptions in the growth hormone/insulin-like growth factor-1 signalling axis, can lead to downstream anabolic–catabolic uncoupling and subsequent muscle wasting, further exacerbating these conditions. Cachexia, one of five key aspects of traditional frailty models, also contributes to the muscle wasting and tissue loss commonly seen in advanced HF. It is officially defined as the loss of more than 5% of total body weight within the previous 6 months. Compared to people without HF, those with HF are 20% more likely to experience sarcopenia. This muscle loss is independent of age and is linked to poorer health outcomes for individuals with HF.[5]

Socioeconomic Factors Affecting Frailty

A recent study found significant disparities in the management and outcomes of frailty in HF patients driven by socioeconomic status. Patients in lower-income brackets were 40% more likely to experience advanced frailty due to delayed medical interventions, reduced access to quality healthcare and malnutrition. These findings underscore the importance of policy interventions aimed at reducing these disparities through expanded healthcare access and community-based support programs.[24]

Socioeconomic factors, such as low income, limited access to healthcare and poor education, are directly linked to the development and progression of frailty in HF patients.[25] Patients from lower socioeconomic backgrounds often lack access to preventative healthcare and nutritious food, contributing to malnutrition, a key driver of frailty.[26] Studies have shown that nutritional deficiencies, especially in protein and essential micronutrients, exacerbate muscle loss and functional decline in frail patients.[27]

Social isolation is another critical factor linked to higher psychological stress, which exacerbates frailty. Studies have shown that individuals with limited social support are more vulnerable to frailty-related complications as they are less likely to engage in physical activity and are more prone to depression and anxiety.[20] Furthermore, individuals who live alone or lack a support network may experience delays in receiving medical care, which can worsen their condition and lead to hospitalisation.[28] Addressing these socioeconomic disparities through policy interventions and support programs could mitigate the impact of frailty on HF outcomes.[28]

Social support networks have been shown to significantly reduce the impact of frailty in HF patients. Those with stronger social connections exhibit slower progression of frailty symptoms and are more likely to adhere to medical and lifestyle interventions.[29] Conversely, social isolation has been shown to significantly worsen frailty outcomes in HF patients.

Table 1: Comparison of Frailty Assessment Tools in Heart Failure

Assessment Tool	Description	Assessment Components	Advantages	Limitations
Fried Frailty Criteria	Identifies frailty based on a physical phenotype	Unintentional weight loss, exhaustion, low physical activity, slowness, weakness	Simple to administer; widely used in research	Limited to physical components; may not capture full frailty spectrum
Frailty Index	Cumulative deficit model considering various health deficits	Comprehensive geriatric assessment across multiple domains	Comprehensive; includes a broad range of health deficits	Time-consuming; requires detailed health information
Clinical Frailty Scale	9-point scale assessing overall fitness and frailty	Clinical judgement based on fitness, comorbidities, functional ability	Quick and easy to use; applicable in clinical settings	Subjective; relies on clinical judgement
Short Physical Performance Battery	Performance-based assessment of lower extremity function	Balance tests, gait speed, chair stand	Objective, performance-based measures	May require equipment and space

Table 2: Overview of Multidimensional Management Strategies for Frailty in Heart Failure

Strategies	Outcomes
Exercise and Rehabilitation	
• Resistance and aerobics training • Cardiac rehabilitation	• Improves muscle strength and endurance • Maximises cardiovascular function and exercise tolerance • Reduces inflammation and hospitalisation rates
Multidisciplinary Care	
• Cardiovascular, geriatric and social help • Physical therapy • Nutritional support	• Improves care coordination, patient satisfaction and clinical outcomes • Mitigates the impact of social isolation and depression
Nutritional Interventions	
• Protein, caloric and vitamin D supplementation • Rectifying micronutrient and omega-3 fatty acid deficiencies • Intravenous iron therapy	• Boosts health outcomes, physical function, exercise capacity, quality of life, functional outcomes and overall prognosis • Enhances muscle repair • Reduces fall risk, frailty severity and hospitalisation rates
Pharmacological Interventions	
• Deprescribing unnecessary medications • Targeted pharmacological interventions • Regular monitoring of renal parameters and potassium levels • Using statins, anti-inflammatory agents, SGLT2 inhibitors and IL-1β inhibitors	• Minimises drug-related risks • Personalises medications to the unique needs of frail patients • Reduces inflammation and oxidative stress • Lowers patient hospitalisation rates • Slows the progression of frailty • Enhances quality of life

IL-1β = interleukin-1β; SGLT2 = sodium–glucose cotransporter 2.

Individuals who lack social support are more likely to experience rapid physical decline and have a higher risk of hospitalisation. Community-based programs that provide social engagement opportunities for frail HF patients are being explored as potential interventions to reduce the impact of social isolation.[30]

Assessment Tools

An important advance in clinical management is the implementation of frailty syndrome assessment into routine clinical practice to improve risk stratification and treatment targeting. Integrating frailty assessment tools into a comprehensive patient evaluation is essential for tailoring management strategies to individual needs. Tools such as the Frailty Index provide detailed insights into multidimensional frailty, while simpler tools such as the Clinical Frailty Scale enable rapid bedside assessments. Combining these methods allows for a holistic understanding of frailty in diverse clinical settings.[31] The following are tools for examining frailty syndrome:

- **Fried Frailty Criteria**: this tool assesses frailty based on five indicators – unintentional weight loss, exhaustion, low physical activity, slowness and weakness. Patients meeting three or more criteria are classified as frail. This tool is simple to administer and has been widely validated in both research and clinical settings. However, its focus on physical aspects of frailty potentially underestimates frailty in HF patients experiencing significant cognitive and social impairments. Despite this limitation, it remains a popular choice for studies emphasising physical function.[28,32]
- **Frailty Index (FI)**: based on the cumulative deficit model, the FI assesses a broad range of health deficits. This multidimensional tool provides a comprehensive measure of frailty severity, making it particularly relevant for HF patients with multiple comorbidities. However, its complexity and the time required for assessment can hinder its routine use in fast-paced clinical settings. The FI has shown strong predictive value for adverse outcomes in older HF populations.[28,33]
- **Clinical Frailty Scale (CFS)**: this 9-point scale ranges from 1 (very fit) to 9 (terminally ill) and uses clinical judgement to assess frailty based on fitness, comorbidities and functional ability. The CFS is efficient and correlates well with other frailty tools, making it particularly useful in clinical practice for predicting adverse outcomes in HF patients. Nevertheless, its reliance on clinician judgement can introduce variability, especially when used by less experienced providers. Recent reviews advocate for the widespread use of CFS due to its practicality and strong predictive validity.[28,34]
- **Short Physical Performance Battery (SPPB)**: this performance-based tool assesses lower extremity function through balance, gait speed and chair stand tests. The SPPB is highly objective and excels in tracking functional changes over time, making it valuable for evaluating physical performance in HF patients. However, it requires equipment and space for administration, which may limit its feasibility in certain settings. It has been validated as a predictor of hospitalisation risk in HF patients.[28,35]
- **Edmonton Frail Scale (EFS)**: a comprehensive tool for rapid screening, covering cognitive function, general health status, functional independence, social support, medication use, nutrition, mood and continence. The EFS offers a broad perspective on frailty, making it suitable for initial screenings where multidimensional impairments are suspected. Despite its versatility, it may oversimplify severe frailty cases and has limited validation specifically in HF populations. EFS remains a useful option for capturing the broader impacts of frailty beyond physical symptoms.[6,36]

While these tools offer valuable insights into frailty assessment, their application in clinical practice is not without challenges. For example, the FI, although comprehensive, can be time-consuming and requires detailed patient data, making it less feasible in resource-limited or fast-paced settings.[33] In contrast, tools such as the CFS are quick and practical but rely on subjective clinician judgement, which may introduce variability.[34] Similarly, performance-based tools such as the SPPB demand specific equipment and adequate space, which might limit their use in certain settings.[35] Adapting these tools to diverse patient populations and healthcare systems remains an ongoing challenge. Future efforts should focus on streamlining these assessments while maintaining their accuracy and relevance in various clinical contexts.

Recent reviews have compared different frailty assessment tools, highlighting the CFS as particularly effective in predicting adverse outcomes in HF patients and advocating for its widespread use in clinical practice (*Table 1*).[28] Emerging technologies, such as wearable devices and biomarker integration, further complement traditional tools by enabling real-time monitoring of physical activity, gait speed and inflammatory markers such as IL-6 and CRP. These innovations hold promise for improving precision in frailty assessment and tailoring interventions for HF patients.[28]

Management Strategies

Managing frailty in HF requires a multidimensional approach incorporating medical, nutritional, physical and psychosocial interventions. Recent research on frailty emphasised individualised exercise programs, nutritional supplementation and careful medication management to improve outcomes.[28] A comprehensive summary of management strategies is presented in *Table 2*, providing an overview of key interventions and their outcomes.

Exercise and Rehabilitation

Recent evidence highlights the effectiveness of exercise-based interventions, particularly resistance and aerobic training, in reversing frailty in HF patients.[37] These programs improve muscle strength, endurance and cardiovascular function and reduce inflammation, contributing to enhanced physical capacity and quality of life.[38] Structured exercise training, such as cardiac rehabilitation, significantly improves exercise tolerance and reduces hospitalisation rates. The combination of aerobic and resistance training is especially effective in improving muscle strength and overall outcomes for frail HF patients.[39]

Nutritional Interventions

Dietary plans that account for the specific nutritional needs of HF patients play a crucial role in managing frailty. Nutritional interventions, including protein, omega-3 fatty acids and caloric supplementation, help mitigate frailty, improve health outcomes and enhance overall quality of life.[6,40] Protein and vitamin D supplementation are essential in frailty management to enhance muscle repair, improve physical function and reduce fall risk in HF patients.[41,42] Addressing micronutrient deficiencies is also essential, advocating for tailored nutritional plans to support overall health.[28]

Iron Deficiency and Anaemia

Iron deficiency anaemia is a highly prevalent comorbidity in patients with HF, particularly among those with frailty and CKD.[43] Iron deficiency impairs oxygen delivery, worsens fatigue and accelerates physical decline. Intravenous iron therapy significantly improves exercise capacity, enhances quality of life and reduces hospitalisation rates in this population.[44,45] Current guidelines recommend routine screening and correction of iron deficiency as an integral part of comprehensive care for frail HF patients, with targeted interventions designed to improve functional outcomes and overall prognosis.[46]

Pharmacological Interventions

Polypharmacy, defined as the use of multiple medications, is prevalent among HF patients and has been linked to increased frailty and adverse health outcomes. Frail patients taking multiple medications face a heightened risk of adverse drug reactions which can worsen HF management and overall prognosis. Strategies to reduce polypharmacy, such as deprescribing unnecessary medications, have shown potential in improving outcomes by minimising drug-related risks and addressing the unique needs of frail patients.[47,48] Personalised medicine plays a critical role here, focusing on careful medication optimisation to balance efficacy and safety while targeting comorbid conditions.[6] Targeted pharmacological interventions addressing inflammation and oxidative stress offer additional avenues for managing frailty.

In frail HF patients with CKD, the use of angiotensin-converting enzyme inhibitors can be challenging due to the increased risk of hyperkalaemia and worsening renal function. Regular monitoring of renal parameters and potassium levels is critical to ensure safety.[49] For instance, the use of statins and anti-inflammatory agents has demonstrated effectiveness in mitigating inflammatory processes linked to frailty.[9] Sodium–glucose cotransporter 2 inhibitors, initially developed for diabetes management, have shown promise in frail HF patients by improving cardiovascular and renal outcomes, reducing inflammation and lowering hospitalisation rates. Tailored dosing and careful monitoring of hydration and renal function are essential, particularly in patients with advanced CKD.[50,51] Emerging therapies focusing on mitochondrial function and oxidative stress reduction, such as interleukin-1β inhibitors, are also under investigation for their potential to slow the progression of frailty and enhance quality of life.[52]

Multidisciplinary Care

Effective frailty management in HF requires a multidisciplinary approach with input from cardiologists, geriatricians, dietitians, physical therapists and social workers. Integrated care models address the complex needs of frail HF patients, improving care coordination, patient satisfaction and clinical outcomes.[28,48] Psychosocial interventions, such as counselling and social support, help mitigate the effects of social isolation and depression on frailty.[16] Multidisciplinary care that combines physical, nutritional and psychological support has proven particularly effective in reducing frailty in HF patients.[50]

Future Directions and Research

Emerging research into the genetic underpinnings of frailty in HF patients suggests that specific gene variants associated with inflammation, muscle metabolism and mitochondrial function may predispose individuals to frailty. Understanding these genetic factors could lead to personalised treatment strategies that better address the unique needs of frail HF patients.[20]

Telemedicine and digital health technologies show great potential in managing frailty in HF, particularly through wearable devices and remote monitoring.[40] Wearable technologies, such as fitness trackers and smartwatches, enable continuous tracking of frailty markers, such as physical activity, heart rate variability and sleep patterns. This real-time data allows healthcare providers to assess frailty in a timely fashion and tailor interventions, which early studies have shown to reduce

hospitalisations and improve health outcomes in frail HF patients.[53,54] Moreover, telemedicine allows for early interventions and personalised care by enabling remote monitoring of medication adherence.

Further studies are needed to evaluate the effectiveness of integrated care models, particularly in diverse healthcare settings. There is also a need for longitudinal studies to assess the long-term impacts of multifaceted intervention programs on frailty and HF outcomes. Understanding the socioeconomic factors that influence frailty and HF outcomes is also essential for developing equitable healthcare strategies that provide targeted support for vulnerable populations.[20] Collaborative research across disciplines and countries could lead to the development of universal guidelines for managing frailty in HF, ultimately improving patient care globally.[10]

Conclusion

Frailty in heart failure patients is a complex, multifactorial condition influenced by physiological, socioeconomic and clinical factors. This syndrome, characterised by inflammation, sarcopenia, neurohormonal dysfunction and oxidative stress, significantly reduces patients' physiological reserve, making them more susceptible to adverse outcomes. Effective management requires a multidisciplinary approach that integrates medical, nutritional, physical and psychosocial interventions to address the complex needs of frail HF patients.

Key strategies for managing frailty include structured exercise programs, tailored nutritional supplementation and careful pharmacological management. Personalised medicine focused on reducing polypharmacy risks shows promise in improving patient outcomes. Multidisciplinary care models are essential for coordinated, holistic care that meets the diverse needs of frail HF patients. Future research should focus on developing standardised frailty assessment tools specific to heart failure and exploring innovative treatments that target core mechanisms, including inflammation and mitochondrial dysfunction. Additionally, telemedicine and wearable technology offer promising methods for continuous monitoring and timely intervention, especially for remote and underserved populations. Collaborative international research is crucial to establish universal guidelines and improve the quality of care for HF patients globally. ❑

1. Tanaka S, Yamashita M, Saito H, et al. Multidomain frailty in heart failure: current status and future perspectives. *Curr Heart Fail Rep* 2021;18:107–20. https://doi.org/10.1007/s11897-021-00513-2; PMID: 33835397.
2. Denfeld QE, Jha SR, Fung E, et al. Assessing and managing frailty in advanced heart failure: an International Society for Heart and Lung Transplantation consensus statement. *J Heart Lung Transplant* 2024;43:1–7. https://doi.org/10.1016/j.healun.2023.09.013; PMID: 38099896.
3. World Heart Federation. *World heart report 2023: full report*. 2023. https://world-heart-federation.org/resource/world-heart-report-2023/ (accessed 30 October 2024).
4. Emmons-Bell S, Johnson C, Roth G. Prevalence, incidence and survival of heart failure: a systematic review. *Heart* 2022;108:1351–60. https://doi.org/10.1136/heartjnl-2021-320131; PMID: 35042750.
5. Talha KM, Pandey A, Fudim M, et al. Frailty and heart failure: state-of-the-art review. *J Cachexia Sarcopenia Muscle* 2023;14:1959–72. https://doi.org/10.1002/jcsm.13306; PMID: 37586848.
6. Denfeld QE, Winters-Stone K, Mudd JO, et al. The prevalence of frailty in heart failure: a systematic review and meta-analysis. *Int J Cardiol* 2017;236:283–9. https://doi.org/10.1016/j.ijcard.2017.01.153; PMID: 28215466.
7. Witte KK, Patel PA, Walker AMN, et al. Socioeconomic deprivation and mode-specific outcomes in patients with chronic heart failure. *Heart* 2018;104:993–8. https://doi.org/10.1136/heartjnl-2017-312539; PMID: 29386325.
8. Gui XY, Rabkin SW. C-reactive protein, interleukin-6, trimethylamine-N-oxide, syndecan-1, nitric oxide, and tumor necrosis factor receptor-1 in heart failure with preserved versus reduced ejection fraction: a meta-analysis. *Curr Heart Fail Rep* 2023;20:1–11. https://doi.org/10.1007/s11897-022-00584-9; PMID: 36479675.
9. Boulet J, Sridhar VS, Bouabdallaoui N, et al. Inflammation in heart failure: pathophysiology and therapeutic strategies. *Inflamm Res* 2024;73:709–23. https://doi.org/10.1007/s00011-023-01845-6; PMID: 38546848.
10. Pandey A, Kitzman D, Reeves G. Frailty is intertwined with heart failure: mechanisms, prevalence, prognosis, assessment, and management. *JACC Heart Fail* 2019;7:1001–11. https://doi.org/10.1016/j.jchf.2019.10.005; PMID: 31779921.
11. Damluji AA, Alfaraidhy M, AlHajri N, et al. Sarcopenia and cardiovascular diseases. *Circulation* 2023;147:1534–53. https://doi.org/10.1161/circulationaha.123.064071; PMID: 37186680.
12. Shao T, Zhang Y, Tang R, et al. Effects of milrinone on serum IL6, TNFα, Cys-C and cardiac functions of patients with chronic heart failure. *Exp Ther Med* 2018. https://doi.org/10.3892/etm.2018.6672.
13. Hasselbach L, Weidner J, Elsässer A, Theilmeier G. Heart failure relapses in response to acute stresses – role of immunological and inflammatory pathways. *Front Cardiovasc Med* 2022;9:809935. https://doi.org/10.3389/fcvm.2022.809935; PMID: 35548445.
14. Zhang Y, Wang Y, Ke B, Du J. TMAO: how gut microbiota contributes to heart failure. *Transl Res* 2021;228:109–25. https://doi.org/10.1016/j.trsl.2020.08.007; PMID: 32841736.
15. Tzanis G, Dimopoulos S, Agapitou V, Nanas S. Exercise intolerance in chronic heart failure: the role of cortisol and the catabolic state. *Curr Heart Fail Rep* 2014;11:70–9. https://doi.org/10.1007/s11897-013-0177-1; PMID: 24293034.
16. Uchmanowicz I, Wleklik M, Gobbens RJ. Frailty syndrome and self-care ability in elderly patients with heart. *Clin Interv Aging* 2015;10:871–7. https://doi.org/10.2147/cia.s83414; PMID: 26028966.
17. Deichl A, Wachter R, Edelmann F. Comorbidities in heart failure with preserved ejection fraction. *Herz* 2022;47:301–7. https://doi.org/10.1007/s00059-022-05123-9; PMID: 35674774.
18. van der Aart-van der Beek AB, de Boer RA, Heerspink HJL. Kidney and heart failure outcomes associated with SGLT2 inhibitor use. *Nat Rev Nephrol* 2022;18:294–306. https://doi.org/10.1038/s41581-022-00535-6; PMID: 35145275.
19. Lee KS, Park DI, Lee J, et al. Relationship between comorbidity and health outcomes in patients with heart failure: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2023;23:498. https://doi.org/10.1186/s12872-023-03527-x; PMID: 37817062.
20. Freedland KE, Skala JA, Steinmeyer BC, et al. Effects of depression on heart failure self-care. *J Card Fail* 2021;27:522–32. https://doi.org/10.1016/j.cardfail.2020.12.015; PMID: 33358958.
21. Vijay K, Neuen BL, Lerma EV. Heart failure in patients with diabetes and chronic kidney disease: challenges and opportunities. *Cardiorenal Med* 2022;12:1–10. https://doi.org/10.1159/000520909; PMID: 34802000.
22. Bellumkonda L, Tyrrell D, Hummel SL, Goldstein DR. Pathophysiology of heart failure and frailty: a common inflammatory origin? *Aging Cell* 2017;16:444–50. https://doi.org/10.1111/acel.12581; PMID: 28266167.
23. Kalogeropoulos A, Georgiopoulou V, Psaty BM, et al. Inflammatory markers and incident heart failure risk in older adults: the Health ABC (Health, Aging, and Body Composition) study. *J Am Coll Cardiol* 2010;55:2129–37. https://doi.org/10.1016/j.jacc.2009.12.045; PMID: 20447537.
24. Browder SE, Rosamond WD. Preventing heart failure readmission in patients with low socioeconomic position. *Curr Cardiol Rep* 2023;25:1535–42. https://doi.org/10.1007/s11886-023-01960-0; PMID: 37751036.
25. Chen X, Mao G, Leng SX. Frailty syndrome: an overview. *Clin Interv Aging* 2014;9:433–411. http://doi.org/10.2147/CIA.S45300; PMID: 24672230
26. Jha SR, Ha HSK, Hickman LD, et al. Frailty in advanced heart failure: a systematic review. *Heart Fail Rev* 2015;20:553–60. https://doi.org/10.1007/s10741-015-9493-8; PMID: 25982016.
27. Zainul O, Perry D, Pan M, et al. Malnutrition in heart failure with preserved ejection fraction. *J Am Geriatr Soc* 2023;71:3367–75. https://doi.org/10.1111/jgs.18590; PMID: 37706670.
28. Sze S, Pellicori P, Zhang J, et al. Identification of frailty in chronic heart failure. *JACC Heart Fail* 2019;7:291–302. https://doi.org/10.1016/j.jchf.2018.11.017; PMID: 30738977.
29. Schroeter ML, Goduila J, Thiel F, et al. Heart failure decouples the precuneus in interaction with social cognition and executive functions. *Sci Rep* 2023;13:1236. https://doi.org/10.1038/s41598-023-28338-0; PMID: 36690723.
30. Liang YY, Chen Y, Feng H, et al. Association of social isolation and loneliness with incident heart failure in a population-based cohort study. *JACC Heart Fail* 2023;11:334–44. https://doi.org/10.1016/j.jchf.2022.11.028; PMID: 36737310.
31. Boreskie KF, Hay JL, Boreskie PE, et al. Frailty-aware care: giving value to frailty assessment across different healthcare settings. *BMC Geriatr* 2022;22:13. https://doi.org/10.1186/s12877-021-02722-9; PMID: 34979966.
32. Bahat G, Ilhan B, Erdogan T, et al. Simpler modified fried frailty scale as a practical tool to evaluate physical frailty: methodological report for its cross-cultural adaptation and validation. *Exp Gerontol* 2022;166:111887. https://doi.org/10.1016/j.exger.2022.111887; PMID: 35803479.
33. Wleklik M, Denfeld Q, Czapla M, et al. A patient with heart failure, who is frail: how does this affect therapeutic decisions? *Cardiol J* 2023;30:825–31. https://doi.org/10.5603/CJ.a2023.0027; PMID: 37067336.
34. Mendiratta P, Schoo C, Latif R. *Clinical frailty scale*. StatPearls Publishing, Treasure Island, Florida. 2023. PMID: 32644435.
35. Welch SA, Ward RE, Beauchamp MK, et al. The Short Physical Performance Battery (SPPB): A quick and useful tool for fall risk stratification among older primary care patients. *J Am Med Dir Assoc* 2021;22:1646–51. https://doi.org/10.1016/j.jamda.2020.09.038; PMID: 33191134.
36. Navarro-Flores E, de Bengoa Vallejo RB, Losa-Iglesias ME, et al. The reliability, validity, and sensitivity of the Edmonton Frail Scale (EFS) in older adults with foot disorders. *Aging (Albany, NY)* 2020;12:24623–32. https://doi.org/10.18632/aging.202140; PMID: 33349621.
37. Vazquez-Guajardo M, Rivas D, Duque G. Exercise as a therapeutic tool in age-related frailty and cardiovascular disease: challenges and strategies. *Can J Cardiol* 2024;40:1458–67. https://doi.org/10.1016/j.cjca.2024.01.005; PMID: 38215969.
38. Mueller S, Winzer EB, Duvinage A, et al. Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA* 2021;325:542–51. https://doi.org/10.1001/jama.2020.26812; PMID: 33560320.
39. Giallauria F, Piccioli L, Vitale G, Sarullo FM. Exercise training in patients with chronic heart failure: a new challenge for cardiac rehabilitation community. *Monaldi Arch Chest Dis* 2018;88:987. https://doi.org/10.4081/monaldi.2018.987; PMID: 30189716.
40. Djoussé L, Cook NR, Kim E, et al. Supplementation with vitamin D and omega-3 fatty acids and incidence of heart failure hospitalization: VITAL-Heart Failure. *Circulation* 2020;141:784–6. https://doi.org/10.1161/circulationaha.119.044645; PMID: 31709816.
41. Vitale C, Jankowska E, Hill L, et al. Heart Failure Association of the European Society of Cardiology position paper on frailty in patients with heart failure. *Eur J Heart Fail* 2019;21:1299–305. https://doi.org/10.1002/ejhf.1611;

PMID: 31646718.
42. Latic N, Erben RG. Vitamin D and cardiovascular disease, with emphasis on hypertension, atherosclerosis, and heart failure. *Int J Mol Sci* 2020;21:6483. https://doi.org/10.3390/ijms21186483; PMID: 32899880.
43. von Haehling S, Ebner N, Evertz R, et al. Iron deficiency in heart failure: an overview. *JACC Heart Fail* 2019;7:36–46. https://doi.org/10.1016/j.jchf.2018.07.015; PMID: 30553903.
44. Zeidan RS, Martenson M, Tamargo JA, et al. Iron homeostasis in older adults: balancing nutritional requirements and health risks. *J Nutr Health Aging* 2024;28:100212. https://doi.org/10.1016/j.jnha.2024.100212; PMID: 38489995.
45. Oli PR, Shrestha DB, Shikhrakar S, et al. Intravenous iron therapy for iron deficiency in patients with heart failure: an updated systematic review and meta-analysis. *Health Sci* 2023;9:100131. https://doi.org/10.1016/j.hsr.2023.100131.
46. McDonagh TA, Metra M, Adamo M, et al. Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2023;44:3627–39. https://doi.org/10.1093/eurheartj/ehad195; PMID: 37622666.
47. Sukumar S, Orkaby AR, Schwartz JB, et al. Polypharmacy in older heart failure patients: a multidisciplinary approach. *Curr Heart Fail Rep* 2022;19:290–302. https://doi.org/10.1007/s11897-022-00559-w; PMID: 35723783.
48. Abboud A, Gaggin HK. Heart failure and frailty: expanding the gender paradox. *Int J Cardiol* 2021;341:60–1. https://doi.org/10.1016/j.ijcard.2021.07.045; PMID: 34314768.
49. Beldhuis IE, Lam CSP, Testani JM, et al. Evidence-based medical therapy in patients with heart failure with reduced ejection fraction and chronic kidney disease. *Circulation* 2022;145:693–712. https://doi.org/10.1161/circulationaha.121.052792; PMID: 35226558.
50. Uchmanowicz I, Lee CS, Vitale C, et al. Frailty and the risk of all-cause mortality and hospitalization in chronic heart failure: a meta-analysis. *ESC Heart Fail* 2020;7:3427–37. https://doi.org/10.1002/ehf2.12827; PMID: 32955168.
51. Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020;396:819–29. https://doi.org/10.1016/S0140-6736(20)31824-9; PMID: 32877652.
52. Onódi Z, Ruppert M, Kucsera D, et al. AIM2-driven inflammasome activation in heart failure. *Cardiovasc Res* 2021;117:2639–51. https://doi.org/10.1093/cvr/cvab202; PMID: 34117866.
53. Alvarez P, Sianis A, Brown J, et al. Chronic disease management in heart failure: focus on telemedicine and remote monitoring. *Rev Cardiovasc Med* 2021;22:403–13. https://doi.org/10.31083/j.rcm2202046; PMID: 34258907.
54. Haywood HB, Sauer AJ, Allen LA, et al. The promise and risks of mHealth in heart failure care. *J Card Fail* 2023;29:1298–310. https://doi.org/10.1016/j.cardfail.2023.07.005; PMID: 37479053.