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The pattern of the frailty syndrome in chronic heart failure

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ABSTRACT

Introduction. *The coexistence of cardiovascular diseases and frailty has been demonstrated, with the prevalence of frailty ranging from 19% to 76%. The presence of frailty significantly influences decision-making regarding the type and timing of diagnostic strategies.*

Objectives. *To assess the features of frailty syndrome in patients with heart failure.*

Material and methods. *A comprehensive search was conducted in PubMed, Google Search, and ResearchGate databases using the keywords "frailty", "heart failure", following the STROBE criteria and PRISMA recommendations.*

Outcomes. *The first publication on frailty syndrome in patients with heart failure dates back to 2007, with research in this area peaking in 2021. The prevalence of frailty in heart failure varies due to differences in age groups, assessment methods, and study designs. Frailty affects approximately 70% of heart failure patients over 80 years of age, challenging the stereotype that frailty is solely associated with elderly individuals. Recently issued data by the World Health Organization (WHO) stated that although frailty and heart failure are common in older adults, the prevalence of frailty in this category of patients is independent of age. It is worth noting that frailty is more common in women, yet women tend to have a better prognosis. Diagnosing frailty in heart failure patients is challenging due to the overlap of clinical symptoms. The interaction between heart failure and frailty increases the risk of decompensation, dependency, and negative outcomes.*

Conclusions. *Previous studies have primarily focused on frailty in elderly patients with heart failure. However, chronological age cannot represent an independent parameter in the assessment of frailty, and patients with heart failure should be assessed for the presence of frailty sovereignly of age for prudent risk stratification. Recognizing and early identification of frailty across all age groups will improve prognosis by reducing hospitalizations and enhancing quality of life.*

Keywords: prevalence, frailty domains, comorbidities, age, sex, outcomes

INTRODUCTION

Cardiovascular disease remains the leading cause of mortality and disability, accounting for one-third of global deaths and is expected to increase by approximately 10% in 2030. As a complex chronic condition, heart failure (HF) affects over 64 million people worldwide, significantly impacting the social, medical, and economic burden [1].

Clinical researches have demonstrated the coexistence of cardiovascular diseases with frailty - a multidimensional syndrome characterized by a decrease in function and physiological reserves, reduced homeostatic tolerance, increased sensitivity, and vulnerability

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to stressors. The concept of frailty is relatively new in medical practice and has been the subject of several discussions. Initially conceived as a purely geriatric syndrome, frailty has been interdisciplinary applied, including in cardiology, over the last decade. Recently issued data by the World Health Organization (WHO) stated that although frailty and heart failure are common in older adults, the prevalence of frailty in this patient category is independent of age. Thus, chronological age cannot serve as an independent parameter in assessing frailty, and patients with heart failure should be assessed for the presence of frailty regardless of age for prudent risk stratification.

The reported prevalence of frailty in heart failure patients varies between 19% and 76%, being more common in patients with heart failure with preserved ejection fraction (HFpEF) compared to reduced ejection fraction (HFrEF) [2-4]. The common pathophysiological mechanisms for heart failure and frailty involve a cascade of neurohormonal, metabolic, inflammatory, and immunological disturbances. The homeostatic imbalance in heart failure exacerbates the decrease in muscle mass and strength, thus benefit the occurrence of sarcopenia, cachexia, and the onset of frailty syndrome (FS). Considering FS can be a decisive factor in the diagnosis and treatment process of patients with cardiovascular diseases. As frailty increases in these patients, an individualized approach is necessary to address deficits in various domains such as physical, cognitive, socioeconomic. Current information on prognosis does not provide clinicians with the most objective insights into disease progression; consequently, prognostic evaluation is rarely used and is informal in clinical practice [5]. The vast majority of clinical research reflects the general population with heart failure, yielding limited results, due to short-term studies and modestly elucidated clinical manifestations, assessment tools, and laboratory features. Thus, the management of frail patients with heart failure remains a challenge for multidisciplinary healthcare teams [6]. Considering that frailty is closely associated with heart failure outcomes such as disability, institutionalization, low quality of life, and premature death, we sought to study the literature that reflects the impact of frailty on the onset and progression of heart failure.

The aim of study: to assess the particularities of frailty syndrome in patients with heart failure.

METHODS

Specialized literature was selected using PubMed, Google Search, and ResearchGate databases, employing the keywords “frailty” and “heart failure” for the period of 2018-2023. The search yielded a total of 16,400 publications mentioning the word “frailty”. After applying the filters and narrowing down the search with the specification “frailty in heart failure”, 345 results were identified. Following a review of the titles and abstracts, 27 full-text articles were selected for further analysis. The literature review was conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) criteria and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

RESULTS

The first publication on frailty syndrome (FS) in heart failure patients emerged in 2007, with a significant peak observed in 2021 (Figure 1).

Prevalence

A review of publications on the prevalence of frailty syndrome (FS) in patients with heart failure (HF) reveals a wide range, varying from 18% to 94% of cases (Table 1).

Studies that specifically assessed physical frailty reported a prevalence of 42.9%, while those that evaluated the psychological and/or social domains, also known as multidimensional frailty, found a frailty prevalence of 47.4% [7]. A meta-analysis of 3,033 participants with heart failure reported a prevalence ranging from 25.4% to 76% [4]. Using data from the TOPCAT trial, a frailty index based on 39 clinical, laboratory, and self-reported variables revealed an impressive frailty prevalence of 94% among heart failure patients with preserved ejection fraction (HFpEF) [8].

More detailed results were obtained from a study involving 467 ambulatory patients with heart failure, which found a prevalence of 52% for physical frailty, 65% for clinical frailty (presence of 5 non-cardiac comorbidities), 39% for social frailty, and 18% for cognitive frailty. Thus, it has been established that the prevalence of frailty syndrome in heart failure varies, which can be attributed to the heterogeneity of age groups, assessment methods, and domains of frailty evaluation in different studies [9].

Pathophysiology

Heart failure and frailty syndrome are complex and interconnected conditions that can manifest independently or in combination. The relationship between frailty and heart failure is of significant interest, as approximately half of heart failure patients are considered frail [10]. The literature explains the frequent occurrence of frailty in individuals with heart failure through shared pathophysiological mechanisms. Inflammatory processes, metabolic abnormalities, and autonomic disturbances are hypothesized to contribute to the development of frailty, leading to decreased skel-

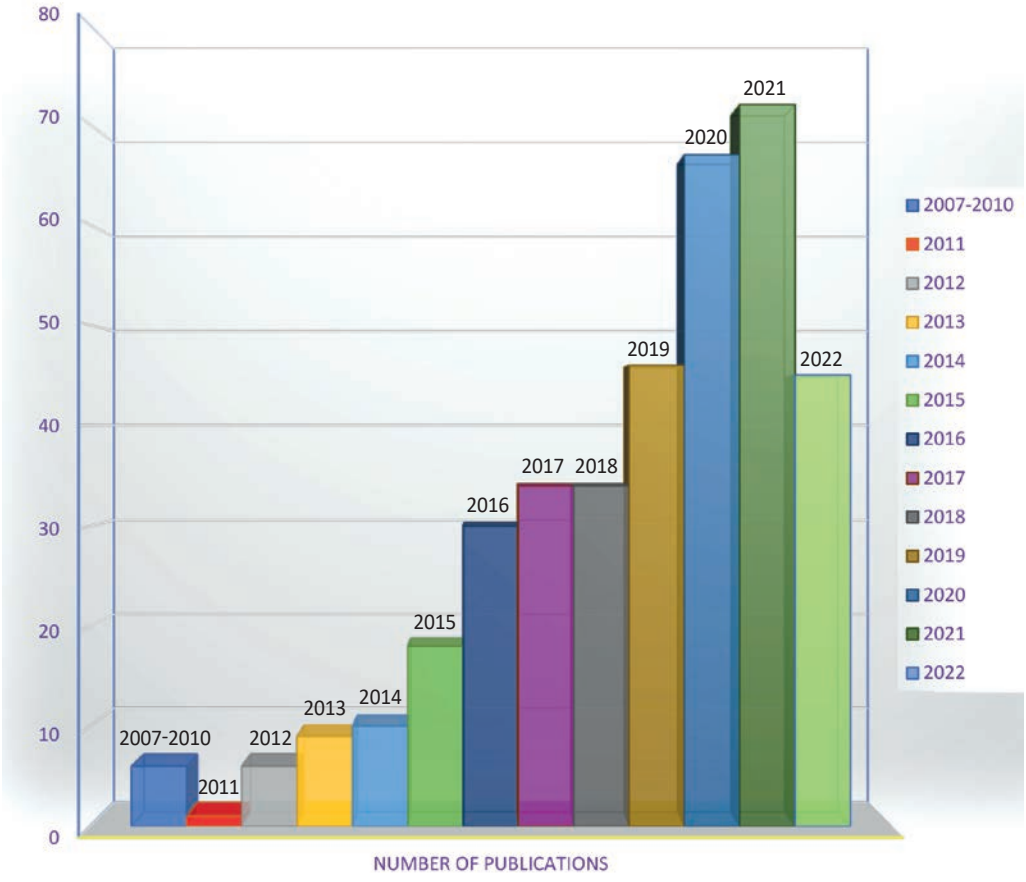

FIGURE 1. *The publication trend of frailty syndrome in heart failure patients from 2007 to 2022*

TABLE 1. *The prevalence of frailty syndrome among patients with heart failure*

Authors, year	Study type	Reporting results
Shirley sze, 2021	Clinic, prospective, randomized, n=460	Physical frailty - 52% Social frailty - 39% Cognitive frailty - 18%
Xige wang, 2018	Meta-analysis n=3033	Frailty syndrome 25,4% - 76,0%
Natalie A. Sanders, 2018	Post-hoc n=1767	All domains frail patients - 94%
Denfeld et al., 2018	Review and meta-analysis n=6896	Physical frailty - 42,9% Psyho-social frailty - 47,4%

etal muscle function and impaired exercise capacity. Cognitive impairments and reduced cerebral perfusion in heart failure patients also increase their vulnerability to falls and accelerate the progression of frailty [11]. Research findings have highlighted the overlapping clinical symptoms between heart failure and frailty syndrome, posing challenges in distinguishing between these two pathological conditions (Figure 2).

Assessment tools

Initially, the diagnostic criteria for frailty proposed in 2001 were based on Fried's phenotype and focused solely on physical frailty, primarily in the context of geriatrics. Fried et al. suggested that the development of frailty is influenced by age-related physiological changes, which manifest as characteristics of physical frailty, including unintentional weight loss, decreased muscle strength and mass, slow walking speed, fatigue, and reduced physical activity. Frailty was defined as the presence of at least three out of five criteria, while the presence of one or two criteria was considered a "pre-frail" state, and the absence of all criteria indicated a "robust" patient (Figure 3).

The correlations between frailty and cardiac pathologies imposed to create a validated score to obtain data on prognosis and the possible interference of frailty therapy with basic treatment in HF. The contemporary model of frailty is based on the accumulation of deficits and recognizes that frailty results not only from physical deficits, but also cognitive disorders, depressive

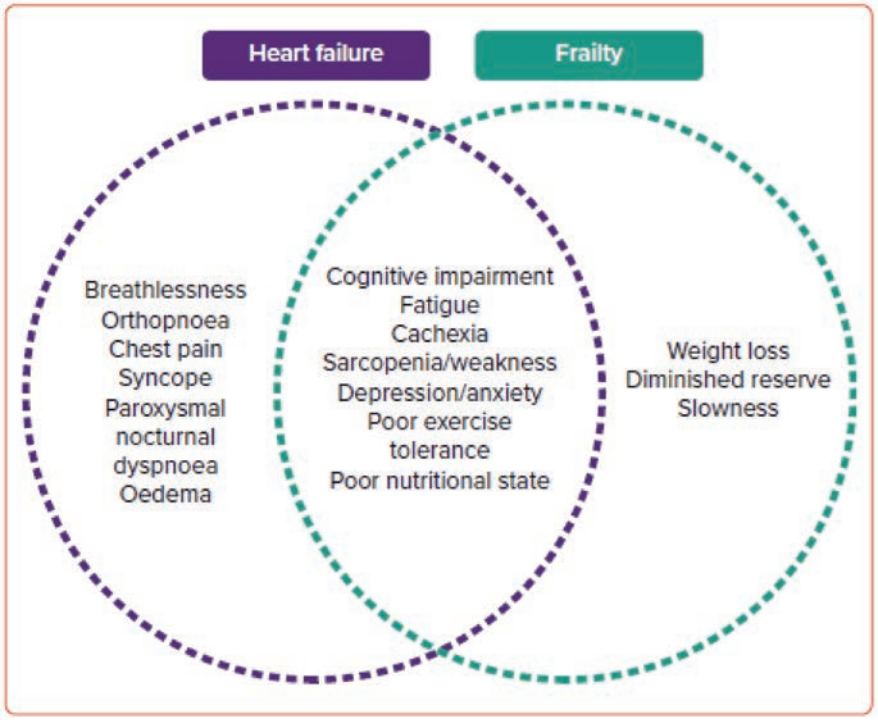

FIGURE 2. *Clinical overlap between frailty and heart failure [26]*

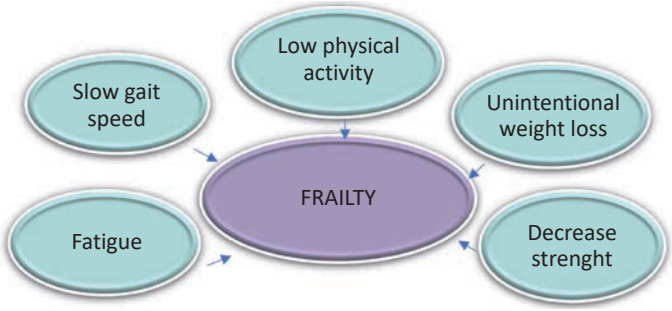

FIGURE 3. *The Fried`s phenotype of frailty*

symptoms, reduced functionality, comorbidities, malnutrition, social isolation, accumulation of whom accelerates the aging [6]. Recently, Sze et al. compared three of the main tools (Fried's phenotype, frailty index and Edmonton frailty score) in HF patients used to identify frailty syndrome. The authors found that more than half of patients tested with a single tool were found to be as frail as those tested with three different tools simultaneously. Misattributing frailty to a patient who is not actually frail or lacking a clear definition of frailty can lead to overestimation of the frailty syndrome and the emergence of frailty. Parallel to ageism, which discriminates against people based on their age, frailty can be defined as a prejudiced stereotype and segregation based on the presence of frailty. This highlights the need for the identification of a relevant instrument to detect frailty in HF patients.

Frailty and age

Numerous publications have examined the correlation between frailty syndrome (FS) and various patient characteristics, including age, sex, presence of risk factors, ejection fraction (EF), and comorbidities. The association between frailty syndrome and age has been extensively studied and established. With the increasing population of individuals aged over 65 years, the coexistence of frailty syndrome and heart failure (HF) is becoming more prevalent. A systematic review and meta-analysis of 3033 elderly patients revealed that frailty was an independent predictor of HF incidence, and the presence of frailty syndrome in this population increased mortality by up to 70% [4]. Frailty affects approximately 70% of HF patients over the age of 80, challenging the stereotype that FS is only associated with HF in the elderly and highlighting the underestimation of frailty in patients under the age of 65. Contemporary research demonstrates that the presence of frailty syndrome and HF is inversely related, independent of age, underscoring the importance of evaluating all patient groups. The LASA study, which followed 1432 adults aged 65-88 years over a period of 17 years, concluded that the risk of frailty is independent of sex, age, and the presence of comorbidities [12].

Gender differences

The prevalence of frailty is higher among women vs. men (62.6% vs. 33.7%) [13,14]. In order to confirm the hypothesis of the influence of gender in frail patients with HF, 2 important studies were conducted. It was found that women had a higher incidence of physical frailty, accounting for 26% . As a confirmation of the obtained data another study achieved similar data (Figure 4). The so-called sex-related paradox was ob-

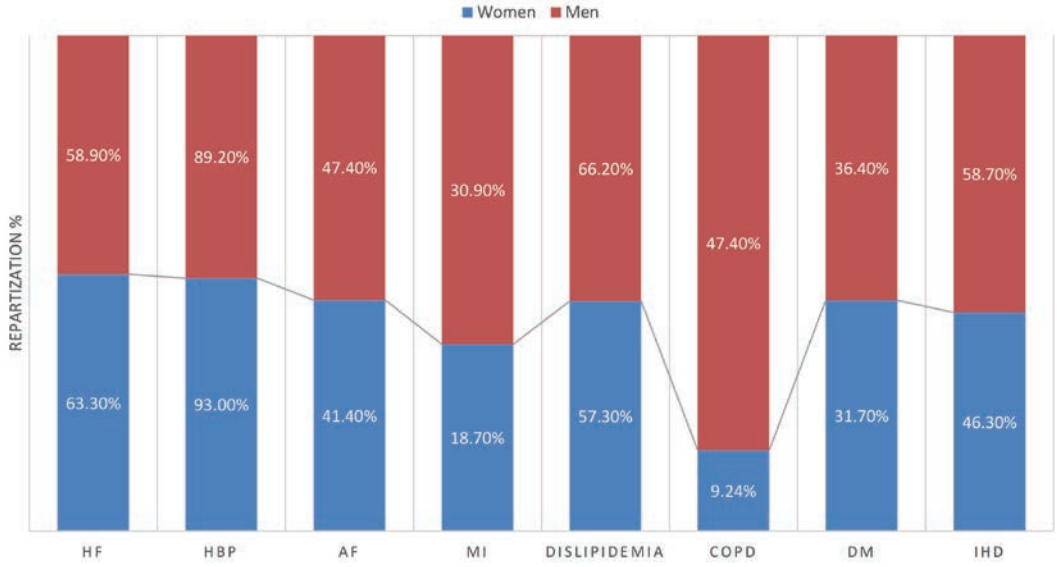

FIGURE 4. *Gender-related differences among frail individuals with heart failure [15,18]*
AF – atrial fibrillation; DM – Diabetes Miletus; HBP – high blood pressure; HF – heart failure; IHD – ischemic heart disease; MI –- myocardial infarction

served in the study recruiting 115 HF patients [15]. While women showed more advanced frailty, their mortality was significantly lower compared to men. The sex difference in the onset of frailty in patients with HF has not been fully studied, although half of adults with HF were women [16]. The incidence of HF doubles in men and triples in women with each decade after age 65. The prevalence of atrial fibrillation among women was slightly lower (41.4% vs. 47.4%), but the rate of hypertension prevailed among women (93.0% vs. 89.2%). Men were more likely to develop myocardial infarction (30.9% vs. 18.7%) with indications for coronary angiography and PCI in 18.9% of cases. Male smokers frequently presented with COPD (47.4%), and experienced sleep apnea, females were more prone to multimorbidity, microvascular coronary disease, concentric left ventricular remodeling, and HF with preserved ejection fraction (HFpEF) with onset at older age. In contrast, men were more likely to have macrovascular coronary disease and develop HF with reduced ejection fraction at a younger age. Women also had a higher frequency of advanced functional class (NYHA III-IV) (38.5% vs. 31.5%). Clinical trials have provided bias data regarding the sex-related paradox and its impact on patient management and prognosis. Some scientific research has shown a better prognosis in women compared to men, while other studies have revealed inverse sex-specific differences [17].

The clinical pattern

The frail population has been observed to have a higher prevalence of abdominal obesity, contradicting the notion that weight loss is associated with frailty [18]. In terms of cachexia in frailty syndrome, its prevalence ranges between 5% and 20% among frail patients with chronic HF [19]. Tsuchida et al. found that the prevalence of sarcopenia and cachexia was 52.6% among patients with worsened chronic HF, with an average age of 64 years [20]. No correlation was detected between ejection fraction and frailty classes [18]. The interaction between cardiovascular pathologies and frailty syndrome (FS) increases the risk of decompensation and dependence, resulting in a complex phenotype with negative outcomes. Frail patients with HF have been shown to be more susceptible to adverse drug reactions, major surgical complications, frequent hospital admissions, increased 1-year mortality, and decreased 10-year survival. Additionally, hospitalizations due to HF exacerbation were longer compared to non-frail patients with HF [21].

More severe frailty was associated with a higher risk of cardiovascular events. The results of a meta-analysis on a sample of 18,757 participants confirmed the hypothesis that frailty in chronic HF is associated with increased mortality (48%) and all-cause hospitalizations (40%). These findings were supported by studies that found frailty in 52.5% of hospitalized patients due to HF exacerbation, and another study conducted on 448 patients with chronic HF demonstrated that 92% of patients presenting to the emergency department were frail, with 65% requiring hospitalization [22,23].

Management of frail patients with heart failure

Cardiac rehabilitation represents a valuable opportunity for the care of frail patients with heart failure (HF). Historically, frail individuals were often excluded from rehabilitation programs due to concerns about their ability to engage in physical exercise. However, re-

cent studies have demonstrated the beneficial effects of rehabilitation and physical activity on the management of frail patients with HF. These interventions have shown positive impacts not only on functional outcomes such as mobility and balance, but also on cognitive and social aspects.

Discussions

Contemporary research and evidence-based clinical practice highlight the significance of frailty syndrome (FS) in the field of cardiology. European cardiology guidelines emphasize the importance of assessing and managing frailty to identify and address its reversible causes [24]. While progress has been made in recognizing frailty among patients with heart failure, a major challenge remains the absence of validated tools for assessing frailty in routine clinical practice [25].

The presence of frailty can significantly impact decision-making regarding diagnostic procedures, timing of interventions, and selection of pharmacological or non-pharmacological treatments. Frail patients with HF are more likely to receive fewer standard HF therapies compared to those without frailty. This treatment disparity arises from the lack of evidence-based guidelines specifically tailored to managing frail patients with heart failure, as clinical trials involving frail individuals are limited [26].

CONCLUSION

The current studies have primarily focused on frailty in elderly patients with heart failure, revealing that frailty is a complex clinical syndrome linked to a higher prevalence of comorbidities. However, research examining frailty in patients under 65 years of age is limited. Recent investigations have indicated sex differences among frail heart failure patients, with a higher incidence of frailty observed in women, while men experience increased mortality and hospitalization rates. Studies have demonstrated that frailty syndrome amplifies the risk of adverse outcomes in heart failure patients, including hospitalizations and mortality. Early identification of the risk of becoming frail ("pre-frail" state) in patients with heart failure allows for prompt multidisciplinary interventions aimed at improving prognosis, outcomes, and management, reducing hospitalizations, and enhancing quality of life. Refining the criteria for defining frailty in patients with heart failure through clinical studies and implementing them in clinical practice will contribute to a more rigorous patient screening and the prescription of safer treatments, thus avoiding the risk of frailtysm.

Conflict of interest: "I undersign, certificate that I do not have any financial or personal relationships that might bias the content of this work."

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