

A patient with heart failure, who is frail: How does this affect therapeutic decisions?

Marta Wleklik^{1,2} , Quin Denfeld³ , Michał Czapla^{2,4,5} , Ewa A. Jankowska^{2,6} ,
Massimo Francesco Piepoli^{6,7,8} , Izabella Uchmanowicz^{1,2} 

¹Department of Nursing and Obstetrics, Faculty of Health Sciences, Wrocław Medical University, Wrocław, Poland

²Institute of Heart Diseases, University Hospital, Wrocław, Poland

³School of Nursing, Oregon Health and Science University, Portland, OR, United States

⁴Department of Emergency Medical Service, Wrocław Medical University, Wrocław, Poland

⁵Group of Research in Care (GRUPAC), Faculty of Health Science, University of La Rioja, Logroño, Spain

⁶Institute of Heart Diseases, Wrocław Medical University, Wrocław, Poland

⁷Dipartimento delle Scienze Biomediche per la Salute, University of Milan, Via Festa del Perdono, Milan, Italy

⁸Cardiology Unit, IRCCS Policlinico San Donato Milanese, Milan, Italy

Abstract

Patients with heart failure (HF) are heterogeneous, not only related to comorbidities but also in the presentation of frailty syndrome. Frailty syndrome also affects patients with HF across the lifespan. Frailty in patients with HF has a significant impact on clinical features, diagnosis, management, adverse medical outcomes and costs. In everyday clinical practice, frail patients with HF require an individualized approach, often imposing the need to modify therapeutic decisions. The aim of this review is to illustrate how frailty and multimorbidity in HF can affect therapeutic decisions.

The scientific evidence underlying this publication was obtained from an analysis of papers indexed in the PubMed database. The search was limited to articles published between 1990 and July 2022. The search was limited to full-text papers published in English. The database was searched for relevant MeSH phrases and their combinations and keywords including: “elderly, frail”; “frailty, elderly”; “frail older adults”; “frailty, older adults”; “adult, frail older”; “frailty, heart failure”; “frailty, multimorbidity”; “multimorbidity, heart failure”; “multimorbidity, elderly”; “older adults, cardiovascular diseases”. In therapeutic decisions regarding patients with HF, additionally burdened with multimorbidity and frailty, it becomes necessary to individualize the approach in relation to optimization and treatment of coexisting diseases, frailty assessment, pharmacological and non-pharmacological treatment and in the implementation of invasive procedures in the form of implantable devices or cardiac surgery. (Cardiol J 2023; 30, 5: 825–831)

Key words: frailty syndrome, heart failure, elderly, multimorbidity, interventions

Introduction

According to the Heart Failure Association, in patients with heart failure (HF), frailty is defined as “a multidimensional dynamic state, independent of

age, that makes the individual with HF more vulnerable to the effect of stressors” [1]. The factors affecting the patient with frailty and predisposing him/her to unfavourable health consequences may be multidimensional, just as the various frailty

Address for correspondence: Dr. Michał Czapla, Wrocław Medical University, ul. Parkowa 34, 51–616 Wrocław, Poland, tel: +48 71 330 77 52, e-mail: michal.czapla@umw.edu.pl

Received: 30.08.2022

Accepted: 29.03.2023

Early publication date: 14.04.2023

This article is available in open access under Creative Commons Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially.

assessments tools are multidimensional (these include the clinical, physical-functional, cognitive-psychological, and social domains of frailty) [1]. Stressors may be clinical or non-clinical, acute or chronic, reversible (i.e., treatable) or irreversible (i.e., require supportive care) [2]. Although the incidence of frailty syndrome (FS) increases markedly with age, people of the same chronological age differ significantly in terms of health status [3]. Chronological age is an important factor in predicting and identifying frailty in an individual; however, frailty is not solely determined by or limited to older chronological age as frailty can present across the lifespan.

Multimorbidity is considered to be the simultaneous occurrence of two or more diseases in the same patient, which increases with age and changes in phenotype. Multimorbidities are usually more chronic in elderly people, contrary to the young [4]. Frailty is not the same as multimorbidity though the presence of comorbidities can exacerbate frailty within an individual [5]. In patients with HF, there is often an overlap between frailty criteria and HF symptoms, as well as the coexistence of old age and multimorbidity [6, 7]. Comorbidities occur to varying degrees in patients with HF and may cause an accumulation of defects that makes patients more vulnerable to stressors, with consequences in terms of negative outcomes and prognosis [8]. HF, together with its associated diseases, needs to be optimized to achieve therapeutic goals, as well as placing a burden on the health system and posing a challenge to global health management [9, 10].

The aim of this paper is to illustrate how frailty and multimorbidity in HF can affect therapeutic decisions.

Methods

The scientific evidence underlying this publication was obtained from an analysis of papers indexed in the PubMed database. The search was limited to articles published between 1990 and July 2022. The search was limited to full-text papers published in English. The database was searched for relevant MeSH phrases and their combinations and keywords including: “elderly, frail”; “frailty, elderly”; “frail older adults”; “frailty, older adults”; “adult, frail older”; “frailty, heart failure”; “frailty, multimorbidity”; “multimorbidity, heart failure”; “multimorbidity, elderly”; “older adults, cardiovascular diseases”.

How to assess frailty? How often to assess frailty?

There are a number of tools to assess FS; however, one of the biggest challenges is selecting the right tool to assess FS [11, 12]. The multitude of tools for FS assessment is caused by the lack of a commonly accepted definition of frailty and, at the same time, the lack of a tool that would be easy to apply in everyday clinical practice and translate into therapeutic decisions [13]. Such an assessment is important both in the context of general internal medicine, but also in the context of qualification for invasive or surgical procedures, where frailty predicts unfavourable clinical outcomes [14]. Martin and O’Halloran [15] suggest that several important aspects should be considered in the context of clinical decision making for frail patients. These include ascertaining suitability for medical or surgical treatment, identifying the best possible method of optimising physiological function, and reducing vulnerability and continued monitoring of clinical progress after treatment [15].

Formal frailty screening should be performed in every HF patient regardless of age or comorbidities. Due to the heterogeneity of FS and the fact that it is a secondary phenomenon to many age-related pathologies, the tools used in FS diagnostics should consider the nature of the HF, it is for this reason that the Heart Failure Association (HFA) Frailty Score, dedicated to patients with HF, has been created [1]. Undoubtedly, the assessment of frailty should not be limited to the physical sphere, but should also cover the psychological and social domains. Although the assessment of frailty is mainly concerned with the physical domain, clinicians should also consider the psychological and social domain of frailty [16].

When using frailty assessment tools, frailty should be identified overall, along with potentially reversible risk factors, such as malnutrition, dehydration, lack of adequate daily physical activity, chronic diseases with cachexia and/or loss of muscle mass, cognitive dysfunction, dementia, depression, reduced functional efficiency in basic and complex life functions, reduced physical activity and mobility, lack of social support, loneliness, institutionalization [1, 17]. The assessment of FS can be performed in everyday clinical practice using simple tools (Table 1) [1, 2, 18–25]. When making clinical decisions in cardiology and cardiac surgery, the assessment of frailty based on the ‘foot-of-the-bed assessment’ or the ‘eyeball test’

Table 1. Tools for assessing frailty in heart failure.

Tools for assessing frailty syndrome	
One-dimensional	Multidimensional
Five meter gait speed [18, 19]	The HFA Frailty Score [1]
Frailty phenotype [20]	The Essential Frailty Toolset [22]
Clinical Frailty Scale [21]	Tilburg Frailty Indicator [23]
	The Edmonton Frail Scale [24]
	Frailty Index [21, 25]

HFA — Heart Failure Association

should be avoided [26]. It has been demonstrated that a fast, clinical assessment at the patient's bedside without objective methods is not reliable in the accurate assessment of frailty [27].

- It should be remembered that the assessment of frailty is important at each stage of HF trajectory [28]. Frailty should be an element of assessment of patients with newly diagnosed HF; the standard assessment should take place during the period of clinical stabilization. Due to changing clinical condition of patients with HF, periodic re-assessment of frailty features is recommended. The assessment of frailty features should also be performed in patients hospitalized due to acute HF, but we should be aware of the limitations of frailty features assessment in patients with cardiovascular instability. Information about frailty status should be documented in the patient's discharge sheet after decompensation; however, re-assessment after full clinical stabilization should be recommended [29].
- Frailty should be considered in the proper selection of diagnostic procedures and the safe implementation of treatment (pharmacological and non-pharmacological) (details below) [2]. The assessment of frailty does not serve as a method to determine the eligibility for treatment but provides information on the patient's sensitivity and potential risk [30].
- It is important to recognize the pre-frail condition in patients in order to be able to implement rehabilitation measures in due time [31]. The keys here are non-pharmacological interventions — motor training, adequate nutrition and hydration, adequate electrolyte and micronutrient supplementation, social

activation. The benefits of this type of intervention for pre-frail and frail older patients affect the reversal of adverse events affecting mobility improvement, reduction of fatigue, improvement of functional capacity, prevention of falls, improvement of quality of life, reduction of depressive symptoms and, most importantly, the possibility of at least partial reversal of frailty [27, 32]. It is always important to assess FS before implementing specific remedial interventions to minimize it (physical training, resistance, polypharmacy, reduction, nutritional support) [33, 34].

- The International Society for Heart Lung Transplantation (ISHLT) highlights the need to identify FS in patients qualified for heart transplantation according to ISHLT transplantation criteria [31].

What should be done with a frail patient with HF who also has multimorbidity?

- It is important to assess whether the frailty is not secondarily related to multimorbidity [35]. To this end, a thorough clinical assessment should be carried out to differentiate frailty from multimorbidity [31].
- The presence of asymptomatic/subclinical, age-related coexisting diseases should be assessed and optimized [10].
- It should be borne in mind that multimorbidity may complicate the interpretation of symptoms of HF and vice versa [36].
- When making therapeutic decisions, it is proposed herein, to take into account the predicted impact of each coexisting disease [37].
- It is worth carrying out the screening assessment for the most common somatic diseases, often asymptomatic (diabetes mellitus, hypertension, renal failure, anemia, iron deficiency, thyroid dysfunction) and implement optimal treatment as required [1].
- Screening for dementia and symptoms indicating depression is worthwhile and optimal treatment should be implemented where applicable [10, 38].
- When making therapeutic decisions, it should be remembered that cognitive dysfunction and depression adversely affect the adherence to therapeutic recommendations in HF [39].
- It is important to assess whether dementia and other disabilities in the patient do not affect the mitigation of treatment and reduce the benefits of evidence-based therapy [39].

- Patients with HF often have a coexisting cancer. When making therapeutic decisions, the need to protect heart function during oncological treatment should be kept in mind [39, 40].

How to manage a frail patient's medications?

Pharmacotherapy in patients with HF should be carefully planned and its implementation should be interdisciplinary, taking into account active support of the patient's family or caregivers in its implementation. This is of particular importance in elderly people and/or those with FS. With regard to pharmacotherapy of individuals with HF with FS, the following measures should be adopted:

- Identify the number of drugs the patient is taking and monitor whether the drugs they are using have proven benefits. Aim to minimize polypharmacy by prioritizing those interventions that improve quality of life. When selecting drugs and adjusting their doses, consideration should be given to factors affecting pharmacokinetics and pharmacodynamics, such as kidney dysfunction, liver dysfunction, hypoalbuminemia, catabolic state, hypovolaemia — common in frail subjects [10, 29, 41–43].
- Patients undergoing diuretic treatment should be particularly monitored for hypovolemia, hyponatremia and hypokalemia as they may lead to pre-renal kidney failure, delirium, and orthostatic hypotension [10].
- Moreover, attention should be paid to patients with hypoalbuminemia whose pharmacokinetics may be impaired, including diuretic treatment with furosemide may be less effective [44].
- Priority should be given to drugs included in European recommendations and with proven efficacy and safety for HF patients with frailty and multimorbidity [10]. It should be stressed that new groups of drugs also have their place in older patients with HF and/or FS.
- The doses of any drugs administered should start from smaller doses and slowly increase to the maximum dose able to be tolerated by the patient [10].
- Monitor the patient for potential adverse effects related to pharmacotherapy. They may be more common in the elderly with frailty and multimorbidity [10]. Consider that drugs used in the treatment of coexisting diseases may have negative effects, e.g., on renal function, thus increasing morbidity and mortality [39].
- Consider that multimorbidity, anorexia, anemia,

hypoalbuminemia, decreased cholesterol levels, anabolic hormone deficiency, iron deficiency, sarcopenia and frailty increase the likelihood of side effects and poor response to treatment [10].

- Apart from direct contact with the patient, telemonitoring solutions should be considered [39].
- Involve family members and caregivers in the process of treatment implementation and monitoring of effectiveness and safety [39].

What should be done when considering implantable devices and cardiac surgery procedures?

With regard to device implantation and invasive or surgical procedures, it is important to carefully consider the potential benefits of the procedure in relation to the patient's remaining life expectancy. When making decisions in this respect, it is important to remember that:

- Age is not, in itself, a contraindication for the implantation of any device or surgical treatment [45].
- In patients with multimorbidity, transcatheter aortic valve implantation should be considered as the preferred method for patients who cannot be surgically repaired or replaced [45].
- Existing diseases are important in decision making by patients considering left ventricular assist device implantation, as they experience an increased conflict of decisions, stress and disease control [46].
- Cardiac patients represent a heterogeneous group in terms of age but also in terms of the number of chronic diseases or psychosocial burdens, therefore identifying those who can benefit most and least remains a significant challenge and requires an individualised approach in preoperative risk assessment [22].
- It is worth identifying subgroups of patients whose invasive and surgical procedures may be futile or even cause a series of complications, deterioration of quality of life and often lead to death [22].

What are other important factors in individualizing the therapeutic process of a patient with HF and FS?

For planning and implementing appropriate measures to prevent the occurrence of FS or to minimize its negative health consequences, a multidimensional approach towards FS fostering individualized interventions for a single pa-

tient with HF is essential [17]. When implementing therapeutic interventions, it is important to remember to: take into account the potential risks and benefits of the interventions, both in regards to HF and multimorbidity and coexistence of FS [36].

- Understand that it is based primarily on the treatment of reversible factors in order to optimise the patient's condition and increase positive results by individualizing the therapeutic plan (treatment, cardiac rehabilitation, nutritional and psychological counselling, education and social support) [2, 29].
- Be conscious that in good therapeutic strategies (pharmacology, implantation of devices, cardiac surgery) and in their implementation, discrimination of patients due to the presence of frailty, is avoided [1, 2].
- Recognize the patient's needs as well as any existing somatic and mental issues during the therapeutic process [10].
- Provide support to the patient, his family members and caregivers [10].
- Talk to patients and their caregivers about their needs and preferences when setting care goals, priorities and therapeutic decisions [36, 39].
- Follow a patient-centred approach even in patients limited by symptoms of advanced HF, combine this with education, collaborative decision-making and discussion of care goals [39, 47].
- Plan a comprehensive patient discharge, taking into account the timing of controls [30, 43]. Discharge planning is one of the most important factors in maintaining medical care, initiated during hospitalization. The change from a hospital to a non-hospital situation requires strict advice on lifestyle counselling in a changing environment [29, 39].
- In the context of complex patient care, it is also important to remember to educate the patient and develop his or her self-care skills [34, 39].

Multidisciplinary Team and Multidisciplinary Approach

The overall therapeutic plan for a patient with HF and FS should be based on a multidisciplinary approach:

- Treatment of patients using the capabilities of an interdisciplinary team of specialists, including in cardiac rehabilitation and palliative care [10, 37, 48].

- The collaboration within the Heart Team is fundamental for a global, holistic assessment of patients with regard to invasive procedures [49].
- Educational and psychological support for patients with HF and depression also outside the period of hospitalization or rehabilitation, which affects the adherence to medical recommendations [46, 50].
- Assessment of frailty in a multidimensional way and making therapeutic decisions, taking into account all its aspects, which enables the HF frailty scale [1, 28].
- In the selection of appropriate intervention or surgical procedures, the decision about less invasive management or abandonment of surgery is always based on a multidisciplinary team decision and focused on the patient, taking into account his goals and values [51].

Conclusions

Multimorbidity, frailty in HF patients has a significant impact on clinical features, diagnosis, management, adverse medical outcomes and costs. Both constructs discussed here should be presented in a multidisciplinary way, building patient-centred strategies in everyday clinical practice. In therapeutic decisions regarding patients with HF, additionally burdened with multimorbidity and frailty, it becomes necessary to individualize the approach in relation to optimization and treatment of coexisting diseases, frailty assessment, pharmacological and non-pharmacological treatment and in the implementation of invasive procedures in the form of implantable devices or cardiac surgery.

Funding

This research was funded by the Ministry of Science and Higher Education of Poland under the statutory grant of the Wrocław Medical University (SUBZ.E250.23.020).

Conflict of interest: None declared

References

1. Vitale C, Jankowska E, Hill L, et al. Heart Failure Association/ European Society of Cardiology position paper on frailty in patients with heart failure. *Eur J Heart Fail.* 2019; 21(11): 1299–1305, doi: [10.1002/ejhf.1611](https://doi.org/10.1002/ejhf.1611), indexed in Pubmed: [31646718](https://pubmed.ncbi.nlm.nih.gov/31646718/).
2. Vitale C, Hill L. Assess frailty but avoid frailtyism. *Eur Heart J Suppl.* 2019; 21(Suppl L): L17–L19, doi: [10.1093/eurheartj/suz239](https://doi.org/10.1093/eurheartj/suz239), indexed in Pubmed: [31885507](https://pubmed.ncbi.nlm.nih.gov/31885507/).
3. Rockwood K, Fox RA, Stolee P, et al. Frailty in elderly people: an evolving concept. *CMAJ.* 1994; 150(4): 489–495, indexed in Pubmed: [8313261](https://pubmed.ncbi.nlm.nih.gov/8313261/).

4. Proietti M, Cesari M. Frailty: what is it? *Adv Exp Med Biol.* 2020; 1216: 1–7, doi: [10.1007/978-3-030-33330-0_1](https://doi.org/10.1007/978-3-030-33330-0_1), indexed in Pubmed: [31894541](https://pubmed.ncbi.nlm.nih.gov/31894541/).
5. Fried LP, Ferrucci L, Darer J, et al. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci.* 2004; 59(3): 255–263, doi: [10.1093/gerona/59.3.m255](https://doi.org/10.1093/gerona/59.3.m255), indexed in Pubmed: [15031310](https://pubmed.ncbi.nlm.nih.gov/15031310/).
6. Denfeld QE, Lee CS. The crossroads of frailty and heart failure: what more can we learn? *J Card Fail.* 2018; 24(11): 733–734, doi: [10.1016/j.cardfail.2018.10.001](https://doi.org/10.1016/j.cardfail.2018.10.001), indexed in Pubmed: [30300685](https://pubmed.ncbi.nlm.nih.gov/30300685/).
7. Kwok CS, Zieroth S, Van Spall HGC, et al. The Hospital Frailty Risk Score and its association with in-hospital mortality, cost, length of stay and discharge location in patients with heart failure short running title: Frailty and outcomes in heart failure. *Int J Cardiol.* 2020; 300: 184–190, doi: [10.1016/j.ijcard.2019.09.064](https://doi.org/10.1016/j.ijcard.2019.09.064), indexed in Pubmed: [31699454](https://pubmed.ncbi.nlm.nih.gov/31699454/).
8. Vitale C, Uchmanowicz I. Frailty in patients with heart failure. *Eur Heart J Suppl.* 2019; 21(Suppl L): L12–L16, doi: [10.1093/eurheartj/suz238](https://doi.org/10.1093/eurheartj/suz238), indexed in Pubmed: [31885506](https://pubmed.ncbi.nlm.nih.gov/31885506/).
9. Wolks E. Heart failure and co-morbidity revisited; the elephant in the room. *Eur J Heart Fail.* 2018; 20(9): 1267–1268, doi: [10.1002/ehfj.1225](https://doi.org/10.1002/ehfj.1225), indexed in Pubmed: [29917297](https://pubmed.ncbi.nlm.nih.gov/29917297/).
10. Jankowska EA, Vitale C, Uchmanowicz I, et al. Drug therapy in elderly heart failure patients. *Eur Heart J Suppl.* 2019; 21(Suppl L): L8–LL11, doi: [10.1093/eurheartj/suz237](https://doi.org/10.1093/eurheartj/suz237), indexed in Pubmed: [31885505](https://pubmed.ncbi.nlm.nih.gov/31885505/).
11. Cesari M, Calvani R, Marzetti E. Frailty in Older Persons. *Clin Geriatr Med.* 2017; 33(3): 293–303, doi: [10.1016/j.cger.2017.02.002](https://doi.org/10.1016/j.cger.2017.02.002), indexed in Pubmed: [28689563](https://pubmed.ncbi.nlm.nih.gov/28689563/).
12. Apóstolo J, Cooke R, Bobrowicz-Campos E, et al. Predicting risk and outcomes for frail older adults: a protocol for an umbrella review of available frailty screening tools. *JBIS Database System Rev Implement Rep.* 2016; 13(12): 14–24, doi: [10.11124/jbis-rir-2015-2468](https://doi.org/10.11124/jbis-rir-2015-2468), indexed in Pubmed: [26767812](https://pubmed.ncbi.nlm.nih.gov/26767812/).
13. Rodríguez-Mañás L, Féart C, Mann G, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. *J Gerontol A Biol Sci Med Sci.* 2013; 68(1): 62–67, doi: [10.1093/gerona/gls119](https://doi.org/10.1093/gerona/gls119), indexed in Pubmed: [22511289](https://pubmed.ncbi.nlm.nih.gov/22511289/).
14. Hamel MB, Henderson WG, Khuri SF, et al. Surgical outcomes for patients aged 80 and older: morbidity and mortality from major noncardiac surgery. *J Am Geriatr Soc.* 2005; 53(3): 424–429, doi: [10.1111/j.1532-5415.2005.53159.x](https://doi.org/10.1111/j.1532-5415.2005.53159.x), indexed in Pubmed: [15743284](https://pubmed.ncbi.nlm.nih.gov/15743284/).
15. Martin FC, O'Halloran AM. Tools for assessing frailty in older people: general concepts. *Adv Exp Med Biol.* 2020; 1216: 9–19, doi: [10.1007/978-3-030-33330-0_2](https://doi.org/10.1007/978-3-030-33330-0_2), indexed in Pubmed: [31894542](https://pubmed.ncbi.nlm.nih.gov/31894542/).
16. Uchmanowicz I, Jankowska-Polanska B, Chabowski M, et al. The influence of frailty syndrome on acceptance of illness in elderly patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2016; 11: 2401–2407, doi: [10.2147/COPD.S112837](https://doi.org/10.2147/COPD.S112837), indexed in Pubmed: [27729781](https://pubmed.ncbi.nlm.nih.gov/27729781/).
17. Wleklik M, Uchmanowicz I, Jankowska EA, et al. Multidimensional Approach to Frailty. *Front Psychol.* 2020; 11: 564, doi: [10.3389/fpsyg.2020.00564](https://doi.org/10.3389/fpsyg.2020.00564), indexed in Pubmed: [32273868](https://pubmed.ncbi.nlm.nih.gov/32273868/).
18. Afilalo J, Eisenberg MJ, Morin JF, et al. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. *J Am Coll Cardiol.* 2010; 56(20): 1668–1676, doi: [10.1016/j.jacc.2010.06.039](https://doi.org/10.1016/j.jacc.2010.06.039), indexed in Pubmed: [21050978](https://pubmed.ncbi.nlm.nih.gov/21050978/).
19. Chen MA. Frailty and cardiovascular disease: potential role of gait speed in surgical risk stratification in older adults. *J Geriatr Cardiol.* 2015; 12(1): 44–56, doi: [10.11909/j.issn.1671-5411.2015.01.006](https://doi.org/10.11909/j.issn.1671-5411.2015.01.006), indexed in Pubmed: [25678904](https://pubmed.ncbi.nlm.nih.gov/25678904/).
20. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001; 56(3): M146–M156, doi: [10.1093/gerona/56.3.m146](https://doi.org/10.1093/gerona/56.3.m146), indexed in Pubmed: [11253156](https://pubmed.ncbi.nlm.nih.gov/11253156/).
21. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ.* 2005; 173(5): 489–495, doi: [10.1503/cmaj.050051](https://doi.org/10.1503/cmaj.050051), indexed in Pubmed: [16129869](https://pubmed.ncbi.nlm.nih.gov/16129869/).
22. Afilalo J, Lauck S, Kim DH, et al. Frailty in older adults undergoing aortic valve replacement: the FRAILTY-AVR study. *J Am Coll Cardiol.* 2017; 70(6): 689–700, doi: [10.1016/j.jacc.2017.06.024](https://doi.org/10.1016/j.jacc.2017.06.024), indexed in Pubmed: [28693934](https://pubmed.ncbi.nlm.nih.gov/28693934/).
23. Gobbens RJJ, van Assen MA, Luijckx KG, et al. The Tilburg Frailty Indicator: psychometric properties. *J Am Med Dir Assoc.* 2010; 11(5): 344–355, doi: [10.1016/j.jamda.2009.11.003](https://doi.org/10.1016/j.jamda.2009.11.003), indexed in Pubmed: [20511102](https://pubmed.ncbi.nlm.nih.gov/20511102/).
24. Graham MM, Galbraith PD, O'Neill D, et al. Frailty and outcome in elderly patients with acute coronary syndrome. *Can J Cardiol.* 2013; 29(12): 1610–1615, doi: [10.1016/j.cjca.2013.08.016](https://doi.org/10.1016/j.cjca.2013.08.016), indexed in Pubmed: [24183299](https://pubmed.ncbi.nlm.nih.gov/24183299/).
25. Robinson TN, Walston JD, Brummel NE, et al. Frailty for surgeons: review of a national institute on aging conference on frailty for specialists. *J Am Coll Surg.* 2015; 221(6): 1083–1092, doi: [10.1016/j.jamcollsurg.2015.08.428](https://doi.org/10.1016/j.jamcollsurg.2015.08.428), indexed in Pubmed: [26422746](https://pubmed.ncbi.nlm.nih.gov/26422746/).
26. Bridgman PG, Lainchbury JG, Hii TBK. Re: Does Frailty Lie in the Eyes of the Beholder? *Heart Lung Circ.* 2015; 24(12): 1238, doi: [10.1016/j.hlc.2015.08.001](https://doi.org/10.1016/j.hlc.2015.08.001), indexed in Pubmed: [26361819](https://pubmed.ncbi.nlm.nih.gov/26361819/).
27. Theou O, Stathokostas L, Roland KP, et al. The effectiveness of exercise interventions for the management of frailty: a systematic review. *J Aging Res.* 2011; 2011: 569194, doi: [10.4061/2011/569194](https://doi.org/10.4061/2011/569194), indexed in Pubmed: [21584244](https://pubmed.ncbi.nlm.nih.gov/21584244/).
28. 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: 283–289, doi: [10.1016/j.ijcard.2017.01.153](https://doi.org/10.1016/j.ijcard.2017.01.153), indexed in Pubmed: [28215466](https://pubmed.ncbi.nlm.nih.gov/28215466/).
29. Martín-Sánchez FJ, Christ M, Miró Ò, et al. Practical approach on frail older patients attended for acute heart failure. *Int J Cardiol.* 2016; 222: 62–71, doi: [10.1016/j.ijcard.2016.07.151](https://doi.org/10.1016/j.ijcard.2016.07.151), indexed in Pubmed: [27458825](https://pubmed.ncbi.nlm.nih.gov/27458825/).
30. Heckman GA, McKelvie RS, Rockwood K. Individualizing the care of older heart failure patients. *Curr Opin Cardiol.* 2018; 33(2): 208–216, doi: [10.1097/HCO.0000000000000489](https://doi.org/10.1097/HCO.0000000000000489), indexed in Pubmed: [29206692](https://pubmed.ncbi.nlm.nih.gov/29206692/).
31. Mauthner O, Claes V, Deschodt M, et al. Handle with care: A systematic review on frailty in cardiac care and its usefulness in heart transplantation. *Transplant Rev (Orlando).* 2017; 31(3): 218–224, doi: [10.1016/j.trre.2017.03.003](https://doi.org/10.1016/j.trre.2017.03.003), indexed in Pubmed: [28390796](https://pubmed.ncbi.nlm.nih.gov/28390796/).
32. de Labra C, Guimaraes-Pinheiro C, Maseda A, et al. Effects of physical exercise interventions in frail older adults: a systematic review of randomized controlled trials. *BMC Geriatr.* 2015; 15: 154, doi: [10.1186/s12877-015-0155-4](https://doi.org/10.1186/s12877-015-0155-4), indexed in Pubmed: [26626157](https://pubmed.ncbi.nlm.nih.gov/26626157/).
33. McDonagh J, Ferguson C, Newton PJ. Frailty assessment in heart failure: an overview of the multi-domain approach. *Curr Heart Fail Rep.* 2018; 15(1): 17–23, doi: [10.1007/s11897-018-0373-0](https://doi.org/10.1007/s11897-018-0373-0), indexed in Pubmed: [29353333](https://pubmed.ncbi.nlm.nih.gov/29353333/).

34. Shinmura K. Cardiac senescence, heart failure, and frailty: a triangle in elderly people. *Keio J Med.* 2016; 65(2): 25–32, doi: [10.2302/kjm.2015-0015-IR](https://doi.org/10.2302/kjm.2015-0015-IR), indexed in Pubmed: [27170235](https://pubmed.ncbi.nlm.nih.gov/27170235/).
35. Abete P, Testa G, Della-Morte D, et al. La comorbilità nell'anziano: epidemiologia e caratteristiche cliniche Comorbidity in the elderly: epidemiology and clinical features. *Giornale di Gerontologia.* 2004; 52.
36. Muth C, Blom JW, Smith SM, et al. Evidence supporting the best clinical management of patients with multimorbidity and polypharmacy: a systematic guideline review and expert consensus. *J Intern Med.* 2019; 285(3): 272–288, doi: [10.1111/joim.12842](https://doi.org/10.1111/joim.12842), indexed in Pubmed: [30357955](https://pubmed.ncbi.nlm.nih.gov/30357955/).
37. Correale M, Paolillo S, Mercurio V, et al. Comorbidities in chronic heart failure: An update from Italian Society of Cardiology (SIC) Working Group on Heart Failure. *Eur J Intern Med.* 2020; 71: 23–31, doi: [10.1016/j.ejim.2019.10.008](https://doi.org/10.1016/j.ejim.2019.10.008), indexed in Pubmed: [31708358](https://pubmed.ncbi.nlm.nih.gov/31708358/).
38. Kim Cy, Duan L, Phan DQ, et al. Frequency of utilization of beta blockers in patients with heart failure and depression and their effect on mortality. *Am J Cardiol.* 2019; 124(5): 746–750, doi: [10.1016/j.amjcard.2019.05.054](https://doi.org/10.1016/j.amjcard.2019.05.054), indexed in Pubmed: [31277789](https://pubmed.ncbi.nlm.nih.gov/31277789/).
39. Böhm M, Coats AJS, Kindermann I, et al. Physiological monitoring in the complex multimorbid heart failure patient: Conclusions. *Eur Heart J Suppl.* 2019; 21(Suppl M): M68–M71, doi: [10.1093/eurheartj/suz232](https://doi.org/10.1093/eurheartj/suz232), indexed in Pubmed: [31908622](https://pubmed.ncbi.nlm.nih.gov/31908622/).
40. Coats AJS. HFA Committee on Comorbidities: Report of a meeting on physiological monitoring in the complex multi-morbid heart failure patient. *Eur J Heart Fail.* 2019; 21(5): 543–544, doi: [10.1002/ejhf.1481](https://doi.org/10.1002/ejhf.1481), indexed in Pubmed: [31069910](https://pubmed.ncbi.nlm.nih.gov/31069910/).
41. Iyngkaran P, Liew D, Neil C, et al. Moving from heart failure guidelines to clinical practice: gaps contributing to readmissions in patients with multiple comorbidities and older age. *Clin Med Insights Cardiol.* 2018; 12: 1179546818809358, doi: [10.1177/1179546818809358](https://doi.org/10.1177/1179546818809358), indexed in Pubmed: [30618487](https://pubmed.ncbi.nlm.nih.gov/30618487/).
42. Rieckert A, Trampisch US, Klaaßen-Mielke R, et al. Polypharmacy in older patients with chronic diseases: a cross-sectional analysis of factors associated with excessive polypharmacy. *BMC Fam Pract.* 2018; 19(1): 113, doi: [10.1186/s12875-018-0795-5](https://doi.org/10.1186/s12875-018-0795-5), indexed in Pubmed: [30021528](https://pubmed.ncbi.nlm.nih.gov/30021528/).
43. Caughey GE, Shakib S, Barratt JD, et al. Use of medicines that may exacerbate heart failure in older adults: therapeutic complexity of multimorbidity. *Drugs Aging.* 2019; 36(5): 471–479, doi: [10.1007/s40266-019-00645-0](https://doi.org/10.1007/s40266-019-00645-0), indexed in Pubmed: [30875020](https://pubmed.ncbi.nlm.nih.gov/30875020/).
44. Gawad MA. Refractory edema with congestive heart failure step-wise approaches nephrology perspectives. *Urol Nephrol Open Access J.* 2014; 1(2), doi: [10.15406/unoaj.2014.01.00011](https://doi.org/10.15406/unoaj.2014.01.00011).
45. Osmanska J, Jhund PS. Contemporary management of heart failure in the elderly. *Drugs Aging.* 2019; 36(2): 137–146, doi: [10.1007/s40266-018-0625-4](https://doi.org/10.1007/s40266-018-0625-4), indexed in Pubmed: [30535931](https://pubmed.ncbi.nlm.nih.gov/30535931/).
46. Warrach HJ, Allen LA, Blue LJ, et al. Comorbidities and the decision to undergo or forego destination therapy left ventricular assist device implantation: An analysis from the Trial of a Shared Decision Support Intervention for Patients and their Caregivers Offered Destination Therapy for End-Stage Heart Failure (DECIDE-LVAD) study. *Am Heart J.* 2019; 213: 91–96, doi: [10.1016/j.ahj.2019.04.008](https://doi.org/10.1016/j.ahj.2019.04.008), indexed in Pubmed: [31129442](https://pubmed.ncbi.nlm.nih.gov/31129442/).
47. Forman DE, Maurer MS, Boyd C, et al. Multimorbidity in older adults with cardiovascular disease. *J Am Coll Cardiol.* 2018; 71(19): 2149–2161, doi: [10.1016/j.jacc.2018.03.022](https://doi.org/10.1016/j.jacc.2018.03.022), indexed in Pubmed: [29747836](https://pubmed.ncbi.nlm.nih.gov/29747836/).
48. Salmon T, Essa H, Tajik B, et al. The impact of frailty and comorbidities on heart failure outcomes. *Card Fail Rev.* 2022; 8: e07, doi: [10.15420/cfr.2021.29](https://doi.org/10.15420/cfr.2021.29), indexed in Pubmed: [35399550](https://pubmed.ncbi.nlm.nih.gov/35399550/).
49. Puri R, Lung B, Cohen DJ, et al. TAVI or No TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation. *Eur Heart J.* 2016; 37(28): 2217–2225, doi: [10.1093/eurheartj/ehv756](https://doi.org/10.1093/eurheartj/ehv756), indexed in Pubmed: [26819226](https://pubmed.ncbi.nlm.nih.gov/26819226/).
50. De Vecchis R, Manginas A, Noutsias E, et al. Comorbidity "depression" in heart failure — Potential target of patient education and self-management. *BMC Cardiovasc Disord.* 2017; 17(1): 48, doi: [10.1186/s12872-017-0487-4](https://doi.org/10.1186/s12872-017-0487-4), indexed in Pubmed: [28196484](https://pubmed.ncbi.nlm.nih.gov/28196484/).
51. Glance LG, Osler TM, Neuman MD. Redesigning surgical decision making for high-risk patients. *N Engl J Med.* 2014; 370(15): 1379–1381, doi: [10.1056/NEJMp1315538](https://doi.org/10.1056/NEJMp1315538), indexed in Pubmed: [24716679](https://pubmed.ncbi.nlm.nih.gov/24716679/).