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EDITORIAL COMMENT

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Assessing frailty in heart failure

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This article refers to 'The prevalence and importance of frailty in heart failure with reduced ejection fraction – an analysis of PARADIGM-HF and ATMOSPHERE' by P. Dewan *et al.*, published in this issue on pages xxx.

I'm not as old as I look!
I thought so!
F. Scott Fitzgerald, 'The Curious Case of Benjamin Button'

Heart failure (HF) is a complex syndrome, being characterized by different causes, precipitators and clinical presentations.[1] A complete characterization of HF would require assessment of additional pathologic processes that lie beyond the cardiovascular system and reflect the systemic implications of the syndrome.[2] In this context, attention has been focused on conditions such as cachexia, wasting, and more recently frailty.[3,4]

Frailty is a state of decreased physiologic reserve and increased vulnerability to acute stressors such as falls, resulting in increased risk of hospitalization and mortality.[4–6] It is generally associated with advanced age,[7] but it also represents a process of accelerated ageing in the context of chronic disease states, in which it affects multiple organ systems and aspects of health, while it is not fully captured by measures of disease severity or progress.

Several tools have been used to screen or assess frailty that can be categorized into two basic approaches.[8] The first one, also termed 'physical frailty phenotype', was developed by Fried *et al.*,[9] who characterized frailty as a physical syndrome depending on five criteria: weak grip strength, involuntary weight loss, exhaustion, slow walking speed, and physical inactivity. The second one, also called the 'cumulative deficit model', was developed by Rockwood *et al.*,[10] who characterized frailty as a more complex syndrome resulting from accumulated physical and non-physical health deficits.

Frailty occurs quite often in patients with HF.[6,11] The Heart Failure Association (HFA) of the European Society of Cardiology recently defined frailty as 'a multidimensional dynamic state, independent of age, that makes the individual with HF more vulnerable to the effect of stressors'.[4] Frailty actually represents accelerated ageing of HF patients, resulting from largely unknown pathophysiology. The proposed mechanisms include immune and hormonal derangement resulting in inflammation, oxidative stress and neurohormonal activation, cellular dysfunction and senescence, sarcopenia, wasting, and others. All these pathologies exist in HF, but it seems that frailty accelerates their expression or evolution.[4]

The overall prevalence of frailty in patients with HF is estimated around 45%, being up to 6 times more frequent in comparison with the general population.[4] Frailty is frequent in HF patients with reduced (HFrEF) and preserved left ventricular ejection fraction, in whom a prevalence as high as 95% was encountered according to the TOPCAT trial.[12] Many of the existing screening or assessment tools have been used in patients with HF (*Table 1*), but there is a lack of recommended ones in this particular population.[8]

In the present issue of the Journal, Dewan and colleagues investigated frailty in a pooled population of HFrEF patients from the PARADIGM-HF and ATMOSPHERE trials.[13] The investigators constructed a 42-item frailty index (FI), based on the Rockwood approach, using multiple health deficits based on patients' history, biomarkers reflecting a wide spectrum of organ systems and 15 questions of the Kansas City Cardiomyopathy Questionnaire. They intentionally avoided to include conventional HF prognosticators such as left ventricular ejection fraction or natriuretic peptides. They managed to construct an index of common health deficits, which are found both in the general population and other diseases,[14–18] rather than an index strictly reflected on HF severity. Patients with FI $\leq$0.210 were classified as non-frail, as previously suggested,[19] while patients with higher scores were divided into two categories using scores increments of 0.100 (0.211–0.310, pre-frail and $\geq$0.311, frail). Importantly, frailty was found to be quite frequent in this selected HFrEF population consisting of relatively young and ambulatory patients with rather mild to moderate symptoms. Out of a total population of 13 625, frailty was present in 63% of patients, a prevalence comparable to that of very elderly

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Table 1 Frailty instruments used in heart failure

Instrument	Developer	Key papers in HF	Domains	Potential use
Cumulative deficit model approach				
Comprehensive Geriatric Assessment (CGA)	Warren, 1946[23] As frailty instrument: Jones *et al.* 2004[24]	Altimir *et al.* 2005[25] Pons *et al.* 2010[26] Rodriguez-Pascual *et al.* 2012[27] Rodriguez-Pascual *et al.* 2014[28]	Functional status, ADL, IADL, comorbidities, cognition, psychological status, communication, social support, nutritional status	Assessment tool
Frailty Staging System (FSS)	Lachs *et al.* 1990[29]	Cacciatore *et al.* 2005[30]	Disability, mobility, cognitive function, visual function, hearing function, urinary continence, social support	Screening tool
Deficit Accumulation Index or Frailty Index (DAI or FI)	Mitnitski *et al.* 2001[14]	McNallan *et al.* 2013[11] Dunlay *et al.* 2014[31] Lupón *et al.* 2008[32]	Self-care ability, dependence on assistive devices, medical conditions, body mass index, depression, ADL, IADL	Assessment tool
Canadian Study of Health and Ageing Clinical Frailty Scale (CSHA-CFS)	Rockwood *et al.* 2005[33]	Parmar *et al.* 2015 [34] Mlynarska *et al.* 2016[35] Sze *et al.* 2017[36]	Level of dependence, functional capacity, comorbidities	Screening tool
Edmonton Frailty Scale (EFS)	Rolfson *et al.* 2006[37]	Sze *et al.* 2019[8]	Cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, functional performance	Assessment tool
Multidimensional Prognostic Index (MPI)	Pilotto *et al.* 2008[38]	Pilotto *et al.* 2010[39]	ADL, IADL, medication use, social aspects, comorbidities, cognition, communication, nutritional status	Assessment tool
Tilburg Frailty Indicator (TFI)	Gobbens *et al.* 2010[40]	Uchmanowicz and Gobbens 2015[41] Uchmanowicz *et al.* 2015[42]	Physical (unexplained weight loss, physical health, difficulty in walking, balance, vision problems, hearing problems, strength in hands, physical tiredness); psychological (cognition, depressive symptoms, anxiety, coping); social (living alone, social relations, social support)	Assessment tool
Derby Frailty Index (DFI)	Woodard *et al.* 2014[43]	Sze *et al.* 2019[8] Sze *et al.* 2017[36]	Age ≥65 and a care home resident, or Age ≥75 and confusion, falls or reduced mobility, or Age ≥85 and >4 comorbidities	Screening tool
Acute Frailty Network criteria (AFN)	Acute Frailty Network, 2018[44]	Sze *et al.* 2019[8]	Age, cognitive impairment, resident in a care home, history of fragility fractures, Parkinson's disease, recurrent falls	Screening tool
Hospital Frailty Risk Score (HFRS)	Gilbert *et al.* 2018[45]	Kwok *et al.* 2020[46]	Administrative hospital data about the patient's medical history	Assessment tool

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Table 1 (Continued)

Instrument	Developer	Key papers in HF	Domains	Potential use
Physical frailty phenotype approach				
Short Physical Performance Battery (SPPB)	Guralnik *et al.* 1994[47]	Chiarantini *et al.* 2010[48] Reeves *et al.* 2016[49] Saitoh *et al.* 2017[50] Warraich *et al.* 2018[51] Pandey *et al.* 2019[52]	Walking speed, balance, chair stand, ADL	Assessment tool
Frailty Phenotype (FP)	Fried *et al.* 2001[9]	Boxer *et al.* 2010[53] McNallan *et al.* 2013[54] Reeves et al. 2016[49] Vidán et al, 2016[55] Moayedi et al, 2018[56]	Weight loss, grip strength, exhaustion, walking speed, physical inactivity	Assessment tool
Survey of Health Ageing & Retirement in Europe Frailty Index (SHARE-FI)	Romero-Ortuno *et al.* 2010[57]	Deek *et al.* 2017[58] Ferguson *et al.* 2017[59] Newton *et al.* 2016[60]	Fatigue, loss of appetite, grip strength, functional difficulties, physical inactivity	Assessment tool
St Vincent's Frailty instrument (SVF)	Jha *et al.* 2016[61]	Jha *et al.* 2016[61] McDonagh *et al.* 2020[62]	Exhaustion, grip strength, mobility, appetite, physical activity	Assessment tool

ADL, activities of daily living; HF, heart failure; IADL, instrumental activities of daily living.

individuals in the general population, which reflects the fact that frailty is associated with accelerated ageing.[4] In addition, frailty conferred an adjusted 63% higher risk of all-cause mortality or hospitalization. These results are in accordance with previous studies, showing similar risk of death and hospitalization in HF patients regardless of age.[4] Notably, the prognostic value of FI was beyond that provided by known prognosticators, such as age, left ventricular ejection fraction, or natriuretic peptides. The FI is thus conceptually diverse from standard risk scores and frailty seems to be more than just a surrogate of advanced syndrome stage according to HF severity measures.

Frailty is not just physical impairment and assessing this domain only may lead to misclassification of HF patients.[4] A holistic multidimensional approach could better determine frailty in HF. In addition, a cumulative deficit approach seems to have a greater value as a predictor of outcomes than the Fried approach.[20,21] In accordance to the above, the HFA[4] has recently proposed the development of a multidimensional assessment tool, adopting a previously suggested approach by Gorodeski and colleagues.[22] This tool includes four domains of interest, the clinical domain (comorbidities, weight loss and falls), the psycho-cognitive domain (cognitive impairment, dementia, depression), the functional domain (impaired activities of daily living, mobility and balance) and the social domain (living alone, institutionalization and lack of social support). The items in each domain remain to be defined. At a later stage this tool needs to undergo validation. However, there are inherited difficulties in the adoption of these or other similar tools in clinical practice given the complexity of the assessment that needs to address several different domains and incorporate numerous variables. This will require engagement of dedicated personnel, with the HF nurse playing a key role, along with information technology-based support, based on electronic health care records as also Dewan and colleagues suggest.

The value of frailty as a predictor of poor outcomes is well described in the current and previous studies. The additive clinical value of measuring frailty in HF patients' monitoring and management requires however further investigations. In this context, the positioning of frailty scales among other surrogates of patient status such as quality of life questionnaires or patient-reported outcomes that are at least partly addressed by cumulative deficit model-based frailty scales, remains to be determined. Frailty measures could potentially be used as additional criteria to refine the indications of device implantation such as implantable cardioverter-defibrillator or to guide interventions such as transcatheter mitral valve repair. At the same time, the appropriate interventions to prevent or treat frailty also remain to be determined. Suggested measures include intensification of disease-specific therapeutic modalities, management of comorbidities, exercise training and other rehabilitation processes and lifestyle interventions. All these approaches have proved effective in improving different aspects of the syndrome, including symptoms, quality of life, morbidity and mortality, but frailty seems to lie beyond these surrogates. The introduction of a widely accepted and validated assessment tool currently attempted by HFA[4] may help in identifying intervention that effectively target the frailty process.

A proposed conceptual framework for frailty in HF is outlined in *Figure 1*. Frailty is not synonymous to ageing, physical impairment or disease severity. It is rather a process of accelerated ageing associated with many chronic pathologies such as HF and affecting multiple organ systems and aspects of health. It seems to be a surrogate of what people calls 'biological age' in contradiction to chronological one. It is yet quite poorly understood, while there are inherited problems in its assessment. Despite the difficulties,

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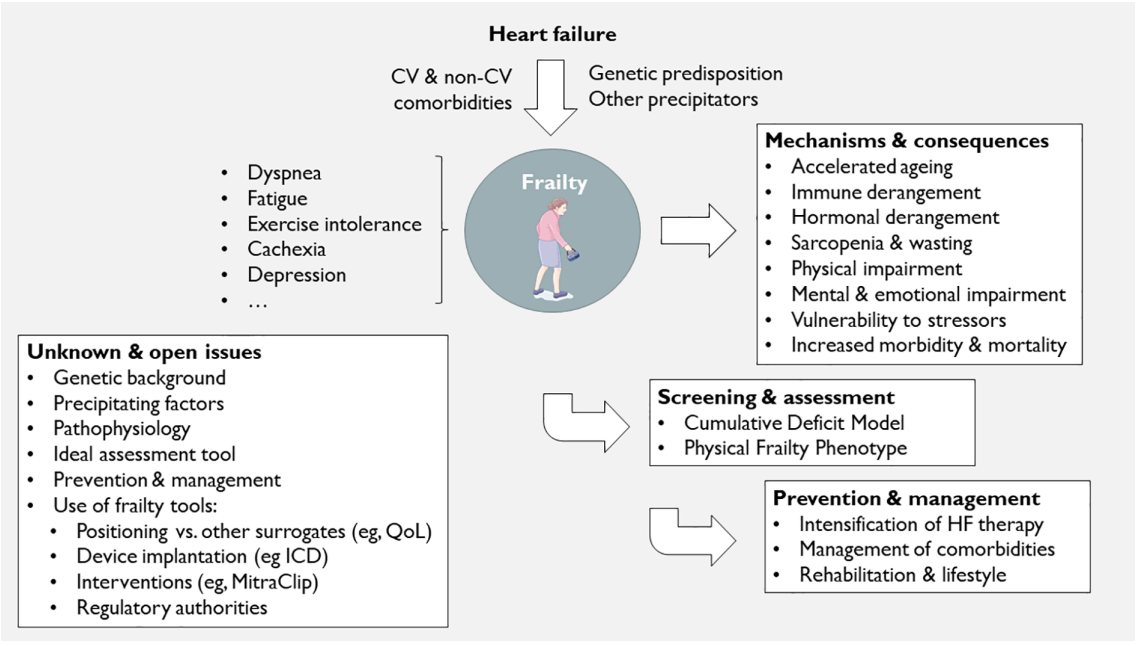

Figure 1 A proposed conceptual framework for frailty in heart failure (HF). CV, cardiovascular; ICD, implantable cardioverter-defibrillator; QoL, quality of life.

the appreciation of frailty will probably open a new window for the better understanding of HF and other syndromes or diseases.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.
Appendix S1. Additional references.

Conflict of interest: D.F. has received modest consultation or lecture fees from Abbott Laboratories, Bayer, Boehringer Ingelheim, Menarini, Novartis, Orion Pharma and Roche Diagnostics. G.F. has served as member of committees in trials sponsored by Bayer, Boehringer Ingelheim, Medtronic, Novartis, Servier and Vifor. M.T. and M.E. have no conflict of interest.

References

1. Filippatos G, Angermann CE, Cleland JG, Lam CS, Dahlstrom U, Dickstein K, Ertl G, Hassanein M, Hart KW, Lindsell CJ, Perrone SV, Guerin T, Ghadanfar M, Schweizer A, Obergfell A, Collins SP. Global differences in characteristics, precipitants, and initial management of patients presenting with acute heart failure. *JAMA Cardiol* 2020;**5**:401–410.
2. Farmakis D, Koeck T, Mullen W, Parissis J, Gogas BD, Nikolaou M, Lekakis J, Mischak H, Filippatos G. Urine proteome analysis in heart failure with reduced ejection fraction complicated by chronic kidney disease: feasibility, and clinical and pathogenetic correlates. *Eur J Heart Fail* 2016;**18**:822–829.
3. Filippatos GS, Anker SD, Kremastinos DT. Pathophysiology of peripheral muscle wasting in cardiac cachexia. *Curr Opin Clin Nutr Metab Care* 2005;**8**:249–254.
4. Vitale C, Jankowska E, Hill L, Piepoli M, Doehner W, Anker SD, Lainscak M, Jaarsma T, Ponikowski P, Rosano GM, Seferovic P, Coats AJ. Heart Failure Association/European Society of Cardiology position paper on frailty in patients with heart failure. *Eur J Heart Fail* 2019;**21**:1299–1305.
5. McDonagh J, Martin L, Ferguson C, Jha SR, Macdonald PS, Davidson PM, Newton PJ. Frailty assessment instruments in heart failure: a systematic review. *Eur J Cardiovasc Nurs* 2018;**17**:23–35.
6. Uchmanowicz I, Loboz-Rudnicka M, Szelag P, Jankowska-Polanska B, Loboz-Grudzien K. Frailty in heart failure. *Curr Heart Fail Rep* 2014;**11**:266–273.
7. Vaughan L, Corbin AL, Goveas JS. Depression and frailty in later life: a systematic review. *Clin Interv Aging* 2015;**10**:1947–1958.
8. Sze S, Pellicori P, Zhang J, Weston J, Clark AL. Identification of frailty in chronic heart failure. *JACC Heart Fail* 2019;**7**:291–302.
9. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;**56**:M146–156.
10. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. *J Gerontol A Biol Sci Med Sci* 2007;**62**:738–743.
11. McNallan SM, Chamberlain AM, Gerber Y, Singh M, Kane RL, Weston SA, Dunlay SM, Jiang R, Roger VL. Measuring frailty in heart failure: a community perspective. *Am Heart J* 2013;**166**:768–774.
12. Sanders NA, Supiano MA, Lewis EF, Liu J, Claggett B, Pfeffer MA, Desai AS, Sweitzer NK, Solomon SD, Fang JC. The frailty syndrome and outcomes in the TOPCAT trial. *Eur J Heart Fail* 2018;**20**:1570–1577.
13. Dewan P, Jackson A, Jhund PS, Shen L, Ferreira JP, Petrie MC, Abraham WT, Desai AS, Dickstein K, Køber L, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, McMurray JJ. The prevalence and importance of frailty in heart failure with reduced ejection fraction – an analysis of PARADIGM-HF and ATMOSPHERE. *Eur J Heart Fail* 2020 Apr 30. https://doi.org/10.1002/ejhf.1832 [Epub ahead of print].
14. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal* 2001;**1**:323–336.
15. Mian HS, Wildes TM, Fiala MA. Development of a Medicare Health Outcomes Survey deficit-accumulation frailty index and its application to older patients with newly diagnosed multiple myeloma. *JCO Clin Cancer Inform* 2018;**2**:CCI.18.00043.

[The remaining references are available in online supplementary Appendix S1]

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