UTS UNIVERSITY OF TECHNOLOGY SYDNEY

The FRAilty MEasurement in Heart Failure (FRAME-HF) Project

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Thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

Under the supervision of Professor Jane Phillips, Associate Professor Caleb Ferguson, and Adjunct Associate Professor Phillip Newton

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Certificate of Original Authorship

I, **Julee McDonagh** declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Faculty of Health at the University of Technology Sydney. This thesis is wholly my own work unless otherwise reference or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution.

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Manuscripts under review

1. **McDonagh J**, Prichard R, Ferguson C, Phillips JL, Davidson PM, Macdonald PS, Newton PJ. Clinician estimates of frailty compared to formal frailty assessment in adults with heart failure: a cross-sectional analysis. 2021; Heart, Lung and Circulation (Under Review).
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3. **McDonagh J,** Ferguson C, Jha SR, Ivynian S, Crossley CJ, Montgomery E, Hwang C, Inglis S, Singh G, Davidson PM, Macdonald PS, Newton PJ. Frailty in hospitalised heart failure patients predicts death and rehospitalisation at 6 months. The Journal of Frailty and Aging. 2017; 5; P117.

Supplementary outputs

Manuscripts

1. Prichard RA, Zhao F-L, **McDonagh J**, Goodall S, Davidson PM, Newton PJ, et al. Discrepancies between proxy estimates and patient reported, health related, quality of life: minding the gap between patient and clinician perceptions in heart failure. Quality of Life Research. Quality of Life Research. 2021; https://doi.org/10.1007/s11136-020-02722-z
2. **McDonagh J**, Ferguson C, Newton PJ. Frailty Assessment in Heart Failure: an Overview of the Multi-domain Approach. Current Heart Failure Reports. Current Heart Failure Reports; 2018; 15(1):17–23.
3. Jha SR, **McDonagh J**, Prichard R, Newton PJ, Hickman LD, Fung E, et al. #Frailty: A snapshot Twitter report on frailty knowledge translation. Australasian Journal on Ageing. Australasian Journal on Ageing. 2018;37(4):309–12.
4. Jha SR, **McDonagh J**, Prichard R, Ferguson C, Macdonald PS, Newton PJ. Commentary response: Frailty, not just about old people: Reply to Smith GD & Kydd A (2017) Getting care of older people right: the need for appropriate frailty assessment? Journal of Clinical Nursing. 2017;26(23-24):4-5.

Book Chapters

1. Jha SR, **McDonagh J**. Assessing measurement instruments In: Whitehead D, Ferguson C, LoBiondo-Wood G, Haber J, editors. Nursing and Midwifery Research. 6. Chatswood, NSW: Elsevier; 2020. p. 210-227.
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Abstract

Background

Frailty is a complex, multifaceted syndrome frequently experienced by older people and those living with chronic disease, such as heart failure. The presence of frailty is a robust predictive indicator of worse outcomes in people with heart failure, including rehospitalisation and mortality. Despite increasing interest in assessing frailty over the last decade, there is an absence of consensus regarding the universal definition of frailty and the optimal means of assessment for this population. Consequently, the clinical recommendations surrounding frailty assessment in patients with heart failure are ambiguous. Given this reality, there is an urgent need to identify the optimal way to assess frailty in a heart failure population.

Aim

The 'FRAilty MEasurement in Heart Failure' (FRAME-HF) project aims to determine the most suitable and clinically relevant frailty instrument(s) for use in adults living with heart failure.

Methods

Setting and participants: The FRAME-HF project was undertaken at St Vincent's Hospital, a global leader in specialised cardiovascular care, located in Sydney, Australia. This project involved two groups of participants: 1) Individuals aged 18 years and older with a confirmed diagnosis of heart failure currently admitted to the cardiology ward or attending the outpatient heart failure clinic, and 2) Cardiovascular clinicians (i.e., registered nurses, physicians, and allied health professionals) providing treatment to patients admitted to the cardiology ward and/or attending the outpatient heart failure clinic.

Design: Deductive sequential mixed methods project comprising three interrelated yet discrete studies: a systematic review (Study 1) explores how frailty has been assessed in heart failure research and elucidates which frailty domains are the most frequently assessed; a cross-sectional study (Study 2) examines the correlation and inter-rater agreement between subjective clinician estimates of frailty and a formal frailty assessment, using a modified version of the Frailty Phenotype in adults with heart failure; and a prospective cohort study (Study 3). The prospective cohort study is the core data

component. It comprises two parts: Part A, which evaluates the validity of three commonly used physical frailty instruments, the Frailty Phenotype, the St Vincent's Frailty instrument and the SHARE-FI; and Part B, which compares the ability of six frailty instruments (the three physical frailty instruments above, as well as, three multi-domain instruments, the Deficit Accumulation Index, the St Vincent's Frailty instrument plus cognition and mood domains, and the FRAIL scale) to predict composite rehospitalisation and mortality at 12 months. Data integration of the three FRAME-HF studies, using narrative and joint display approaches, generated a series of clinical recommendations for future practice and research which can help clinicians implement routine frailty assessment in the heart failure clinical setting.

Results

Study 1: A systematic review identified seven different frailty instruments used to identify frailty in heart failure studies to date, none of which were validated for use in patients living with heart failure. The Frailty Phenotype, a 'physical frailty instrument', was the most commonly used instrument, and physical function the most frequently assessed frailty domain. There is also a lack of consensus and robust evidence regarding which frailty assessment method is most suitable and clinically relevant for adults with heart failure.

Study 2: A cross-sectional study of the association between subjective clinician estimates of frailty and a formal frailty assessment using a modified version of the Frailty Phenotype. Thirty-nine clinicians (nurses, physicians and allied health professionals) completed frailty estimates, and 75 patients had their frailty assessed using the modified Frailty Phenotype, producing 194 paired frailty assessments. This study revealed that correlation and inter-rater agreement between pooled clinician-estimated frailty and the formal frailty assessment was fair (r_s= 0.52; κ= 0.33, CI: 0.23 – 0.43). Correlation and agreement were highest between allied-health estimated and formal frailty (r_s= 0.71; κ= 0.45, CI: 0.22 – 0.68), though this was only moderate. These results confirm that subjective clinician estimates of frailty are not a reliable replacement for formal frailty assessment in adults living with heart failure, emphasising the need for assessment with a valid and reliable frailty instrument.

Study 3: Part A evaluated the convergent and discriminant validity of three physical frailty instruments. Of the three instruments compared, the SHARE-FI and the St Vincent's Frailty instrument displayed stronger validity than the Frailty Phenotype in this cohort. Part B

showed that the six frailty instruments potentially relevant for use in adults living with heart failure displayed adequate predictive performance with C-statistic values between 0.71-0.73 and sensitivity between 88-92%. The SHARE-FI and the Deficit Accumulation Index reported the highest odds for rehospitalisation and mortality at 12 months (OR 2.43 [0.81 -7.24] and 1.66 [0.74 – 3.72], respectively). These results suggest that all six instruments are suitable for risk-stratification and research purposes. However, their applicability for routine clinical care and as part of a frailty management plan is yet to be determined. Data integration revealed that, of the frailty assessment instruments compared in this project, the SHARE-FI might be the most suitable and clinically relevant frailty instrument for use in adults living with heart failure, but these results need confirmation in a larger cohort.

Conclusion

The FRAME-HF project provides important novel information regarding the assessment of frailty in heart failure and has identified several critical areas for future research. Most importantly, a validated frailty instrument for use in people living with heart failure, one that is quick and easy to use in a resource-restricted clinical environment, is required. Further work regarding the preferred setting and time-point in the illness trajectory to assess frailty (i.e., inpatient vs. outpatient) and consensus regarding the definition of frailty and the optimal instrument for use in a heart failure population is needed. The applicability of the instruments evaluated in this project for use in routine clinical care and a frailty management plan is also a high priority for future research. Finally, frailty assessment needs to be incorporated into cardiovascular clinicians' daily practice and universally accepted as an integral part of heart failure clinical management.

Abbreviations

AKPS	Australian-modified Karnofsky Performance scale: a measure used to determine functional capacity, primarily used in palliative care (1).
CGA	Comprehensive geriatric assessment
CSANZ	Cardiac Society of Australia and New Zealand
DMI-10	Depression in Medical illness-10 questionnaire: used to determine the presence of depression in those who are medically ill, with a score of ≥9 (out of 30) indicative of possible or probable depression (2).
eGFR	Estimated glomerular filtration rate
EQ5D-5L	The EuroQoL 5D- 5l questionnaire: used to measure health-related quality of life (3).
FRAIL scale	The Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight scale: a short multi-domain frailty instrument that assesses five domains of frailty to determine the degree of frailty in an individual (frail, pre-frail, or robust) (4).
HF-PEF	Heart Failure with Preserved Ejection Fraction: the heart's inability to fill with blood effectively (5).
HF-REF	Heart Failure with Reduced Ejection Fraction: the heart's inability to pump blood effectively (5).
IMPACCT	Improving Palliative, Aged and Chronic Care through Clinical trials and Translation: a research centre in Sydney, Australia.
LVEF	Left Ventricular Ejection Fraction: a measure obtained from echocardiogram often used to diagnose the type of heart failure (i.e., pumping or filling problem)
MDT	Multidisciplinary team: is a term used to describe various health care professionals from different specialities working together to provide supportive care and case management to individuals, particularly older adults (6).
MoCA	Montreal Cognitive Assessment: a questionnaire delivered to individuals to

	determine the presence of mild cognitive impairment, with a score of ≥ 26 (out of 30) indicative of mild cognitive impairment (7).
NHFA	The National Heart Foundation of Australia
NYHA	New York Heart Association
PICF	Participant Information and Consent Form
ROC curve	Receiver Operating Characteristic curve
SHARE-FI	Survey of Health Ageing and Retirement in Europe Frailty Index: a physical frailty instrument that assesses five physical domains of frailty to determine the degree of frailty in an individual (frail, pre-frail, or non-frail) (8).
SVF	St Vincent's Frailty instrument: a physical frailty instrument that assesses five physical domains of frailty to determine the degree of frailty in an individual (frail, pre-frail, or non-frail) (9).
SVF+	St Vincent's Frailty Instrument plus cognitive and mood domains: a multi-domain frailty instrument that assesses seven domains of frailty to determine the degree of frailty in an individual (frail, pre-frail, or non-frail) (10, 11).

Glossary

Data integration	The process of combining data from multiple research methods and studies to generate knowledge of insight unavailable to single method studies (12).
Deficit Accumulation Index	Deficit Accumulation Index: a multi-domain frailty instrument that assesses frailty according to the number of functional, medical, or social deficits an individual has (13, 14).
Frailty syndrome	A clinically recognisable syndrome of vulnerability to acute stressors, characterised by physical weakness and muscle wastage (15).
The Frailty Phenotype	A physical frailty instrument that assesses five physical domains of frailty to determine the degree of frailty in an individual (frail, pre-frail, or non-frail) (16).
Heart Failure	The heart's inability to fill and/or pump blood effectively due to structural or functional disease (5).
Inpatient	A person who is currently receiving treatment in an acute care facility.
Meta-inference	The overall conclusions, explanations, or understanding developed though combining the inferences obtained from missed methods study (17, 18).
Outpatient	A person who is currently receiving care in the community or clinic setting.
Pre-habilitation	The process of enhancing an individual's functional capacity to enable them to withstand major surgery (19).

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Chapter 1: Introduction

1.1 Preamble

Frailty is complex, multifaceted syndrome frequently experienced by people with heart failure. The comorbidity associated with frailty and heart failure contributes to adverse health outcomes for patients and substantial challenges for treating clinicians. This chapter provides an overview of frailty syndrome, and frailty assessment approaches in the context of heart failure. An overview of the doctoral project, research questions and thesis structure will be provided to conclude.

1.2 Background and significance of health issue

Globally, heart failure affects more than 38 million people (1). In Australia, approximately half a million people live with heart failure (2), which impacts their physical well-being and social, functional, and cognitive health (3). The National Heart Foundation of Australia (NHFA) and Cardiac Society of Australia New Zealand (CSANZ) define heart failure as:

> *…a complex clinical syndrome with typical symptoms and signs that generally occur on exertion, but can also occur at rest (particularly when recumbent). It is secondary to an abnormality of cardiac structure or function that impairs the ability of the heart to fill with blood at normal pressure or eject blood sufficient to fulfil the needs of the metabolising organs (4) (p.1136).*

Heart failure is a significant driver of health care expenditure, with the economic burden in Australia estimated at AUD 1 billion; and $108 billion globally (5, 6). In addition to this economic cost, the impact on families and informal caregivers of some living with heart failure is significant, with many experiencing high-stress levels and poor emotional and physical health (7). For the person living with heart failure, there are also significant impacts depending on their stage of illness, as this is a chronic condition that is associated with high morbidity, including cognitive impairment and frailty; and mortality, particularly in older adults and is one of the leading causes of hospitalisation and primary care consultations globally (3, 8).

1.2.1 Classification of heart failure

The clinical syndrome of heart failure has several typical symptoms, yet many of these are nonspecific. The primary symptom of heart failure is dyspnoea which can manifest as orthopnoea, nocturnal dyspnoea, and exertional dyspnoea (4). Other important typical symptoms include palpitations, fatigue, peripheral oedema, splanchnic and pulmonary congestion, hepatic enlargement, and decreased exercise tolerance (4, 9). Heart Failure is characterised by episodes of clinical deterioration and progressive symptoms, functional and physical decline and ultimately death, despite optimal clinical management (3).

The majority of individuals experience heart failure with reduced ejection fraction (HF-REF), i.e., the inability of the heart to pump blood effectively (10). Ischemic heart disease and previous myocardial infarction are the most common causes of HF-REF, accounting for approximately two-thirds of cases. The second less common type of heart failure is heart failure with preserved ejection fraction, i.e., the inability of the heart to fill with blood effectively (HF-PEF). Individuals with HF-PEF are most often female and more likely to have atrial fibrillation and hypertension than coronary artery disease (10).

The New York Heart Association (NYHA) functional classification (11) provides criteria of which the limitations associated with heart failure can be graded, as outlined below:

- **Class I**: No limitation on ordinary physical activity;
- **Class II**: Slight limitation of ordinary physical activity - no symptoms at rest;
- **Class III**: Marked limitation of ordinary physical activity - no symptoms at rest; and
- **Class IV**: Symptoms on any physical activity or at rest (11).

Heart failure predominately affects older adults aged 65 and older, with prevalence increasing significantly with age (12). While ageing does not cause heart failure, the combination of age-related cardiovascular changes, such as structural and functional changes; diminished cardio-protective and repair processes; increased incidence and prevalence of cardiovascular disease; and systemic disease may contribute to heart failure development (13). Heart failure is hypothesised as

> *…the quintessential final cardiovascular aging pathway, representing the convergence of age-associated changes in cardiovascular structure and function,*

aging changes in other organ systems, and the progressive increase in cardiovascular diseases in the elderly (13) (p.143).

1.2.2 Management of heart failure

Over the past four decades, there has been a significant advancement in both the pharmacological and non-pharmacological management of heart failure, including numerous novel pharmacotherapies, nurse-led medication titration programs, multi-disciplinary disease management programs, implantable cardiac electronic device therapy, percutaneous valvular, and coronary artery disease procedures; and advanced therapies, such as ventricular assist device therapy and heart transplantation (4, 9, 14). Yet, these advancements are associated with high costs and finite resources (15, 16). In a bid to lower the overall economic burden of heart failure, there is growing international attention on reducing rehospitalisation and length of stay, resulting in the careful use of advanced therapies, making the selection of the most appropriate patients for these therapies increasingly important (17).

People living with heart failure present with many defining clinical features; the presence of frailty has become an increasingly dominant comorbid area of concern. Frailty is characterised by 'accelerated ageing' and the failure of homeostatic mechanisms, which manifests as a significant vulnerability in those who are frail (18).

While the global incidence of frailty at the population level is unclear, a 2019 meta-analysis involving a large cohort of community-dwelling adults (n=12, 805) aged over 60 years from 28 countries estimated that the incidence of frailty was 43.4 cases per 1000 person-years (19). Frailty is highly prevalent in people living with heart failure and predictive of worse outcomes, such as rehospitalisation and mortality (20). Over the last decade, there has been growing interest in the role of frailty in heart failure management, both as a predictor of poorer outcomes and a desire to prevent it from occurring (21).

1.3 The origin of frailty as a syndrome

Frail (adjective) was first described in the middle English translation of the bible in approximately 1382 (22). The word *frail* originates from the Old French word *frêle*, meaning 'of little resistance', and the Latin words *fragilis* and *frangere, meaning* 'easily broken' and 'to break' (23). The modern Oxford English dictionary defines frail as "liable to break or be

broken…. Weak, subject to infirmities" (Oxford University Press, online version) (22). The seminal medical definition of *frailty* was conceptualised over two decades ago (24). Consequently, our thinking of frailty has evolved from these earlier origins to now being recognised as a complex multidimensional clinical syndrome.

Frailty is a syndrome characterised by an increased vulnerability to acute stressors, such as falls, infection, and hospitalisation. It is associated with reduced physiological reserve across multiple body systems, loss of independence, and high mortality (25, 26). Frail individuals have a lower level of baseline functionality compared to those who are non-frail. When faced with a minor stressor event, such as a urinary tract infection, they experience a prolonged deterioration and rather than returning to their baseline level of functionality; they deteriorate further towards dependence or disability. In contrast, non-frail individuals, when faced with a minor stressor event, only experience a short deterioration before returning to their baseline level of functionality (Figure 1.1) (27).

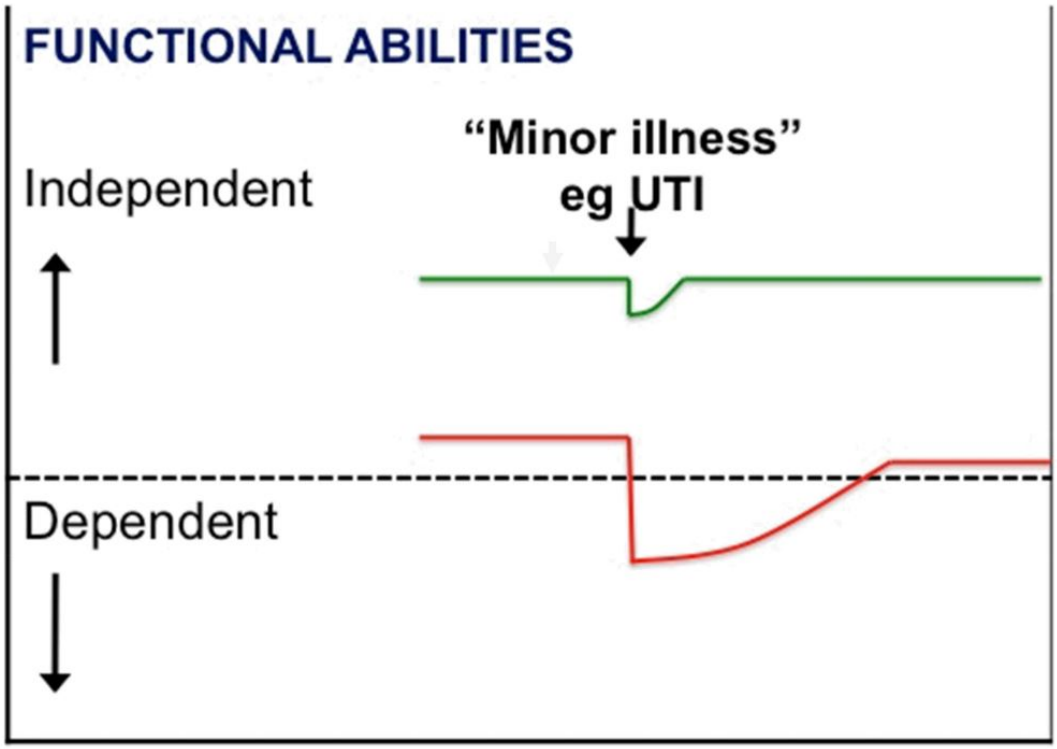

Figure 1-1 Vulnerability of frail older people following a minor illness.

Key: UTI: Urinary tract infection. Image from Clegg et al. (27) (p.20), reused with permission from Elsevier (licence 4953950037379 Nov 21, 2020).

1.3.1 Pathophysiology and aetiology of frailty

The precise pathophysiological processes which contribute to the development of frailty remain unknown (17, 28). However, it is hypothesised as the result of several factors, such as aging and disease processes; genetic, environmental and lifestyle factors; immune/inflammatory pathway activation; and decline across musculoskeletal, endocrine, cardiovascular, neurological and hematologic systems (Refer Figure 1.2) (18). A recent systematic review (2020) also suggests vascular endothelial dysfunction may play a role in the development of frailty, with cross-linking underlying inflammation and oxidative stress found in both frailty and impaired vascular endothelial function (29).

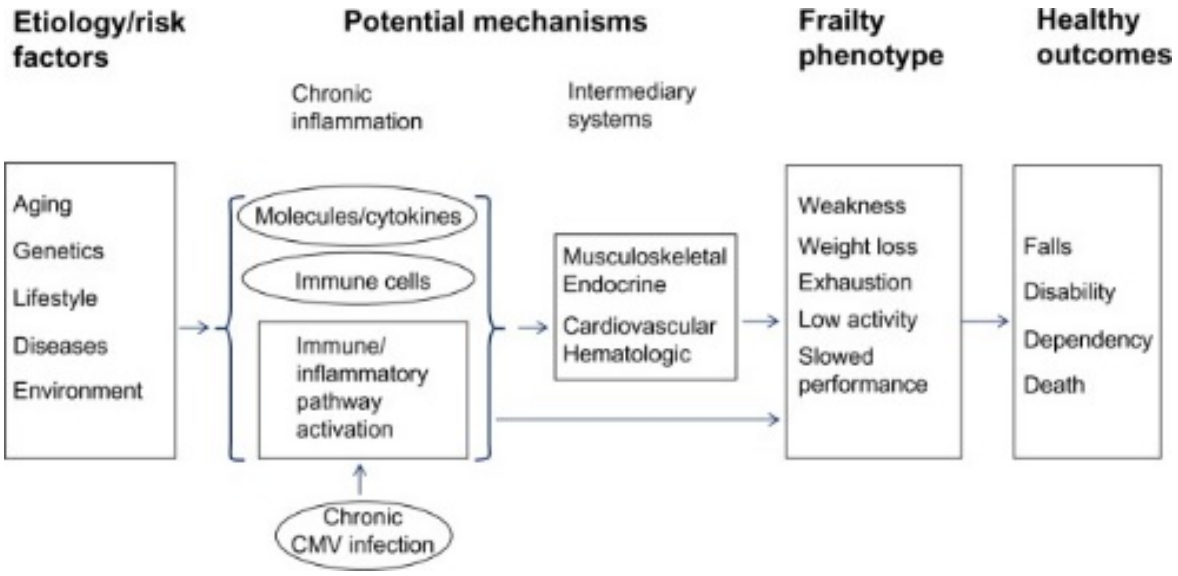

Figure 1-2 The pathogensis of frailty.

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1.4 Conceptualising and assessing frailty

There are generally two broad conceptual models used to define frailty (30), as outlined in Figure 1.3.

1.4.1 Frailty as a biological syndrome

The first model defines frailty as a biological syndrome that results in age-related physical decline; this definition has been widely adopted since the development of the Frailty

Phenotype by Fried and colleagues in 2001 as part of the Cardiovascular Health Study (24). The Frailty Phenotype focuses on physical aspects of frailty and classifies someone as frail if they are positive in three or more out of the following five criteria; weakened handgrip strength slowed walking speed, unintentional weight loss, low physical activity and physical exhaustion (24). Consequently, the Frailty Phenotype is often considered to be the definition of physical frailty. The Frailty Phenotype involves a combination of patient self-reported and clinician assessed components and includes an objective measure of walking speed and handgrip strength (measured via a handgrip dynamometer) (24).

1.4.2 Frailty as a multidimensional syndrome

The second conceptual model of frailty was developed by Rockwood and colleagues and defines frailty as a multidimensional syndrome (rather than a purely physical syndrome) and is assessed through the accumulation of health deficits across multiple domains, such as cognitive, functional, social and medical (31, 32). This accumulative deficit model commonly referred to as the Deficit Accumulation Index (or Frailty Index), is expressed as the ratio of health deficits to the total number of deficits assessed (33). The number of health deficits used to assess frailty is not fixed and can be altered to suit a specific health population or clinical setting. The Deficit Accumulation Index is strongly associated with admission to residential aged care or nursing home and death, particularly if more than thirty deficits are assessed (32). A significant difference between the Frailty Phenotype and the Deficit Accumulation Index is that the latter can be ascertained from the medical records rather than relying on patient self-reported and objective measures and therefore may be more suitable for assessing frailty in large cohorts (34).

1.4.3 Assessing frailty

Since the prolific 'biological driven frailty' and 'deficit driven frailty' conceptualisations, there have now been more than sixty different frailty assessment instruments developed (35). In a recent survey of 388 clinicians across 44 countries, 53% of clinicians reported consistently assessing frailty in their routine clinical practice. Participants were primarily physicians (93%) working primarily in geriatric care (83%) (36). Despite this, there is currently no internationally accepted reference standard or definition of frailty syndrome and no consensus on the 'optimal' means of assessment (37, 38).

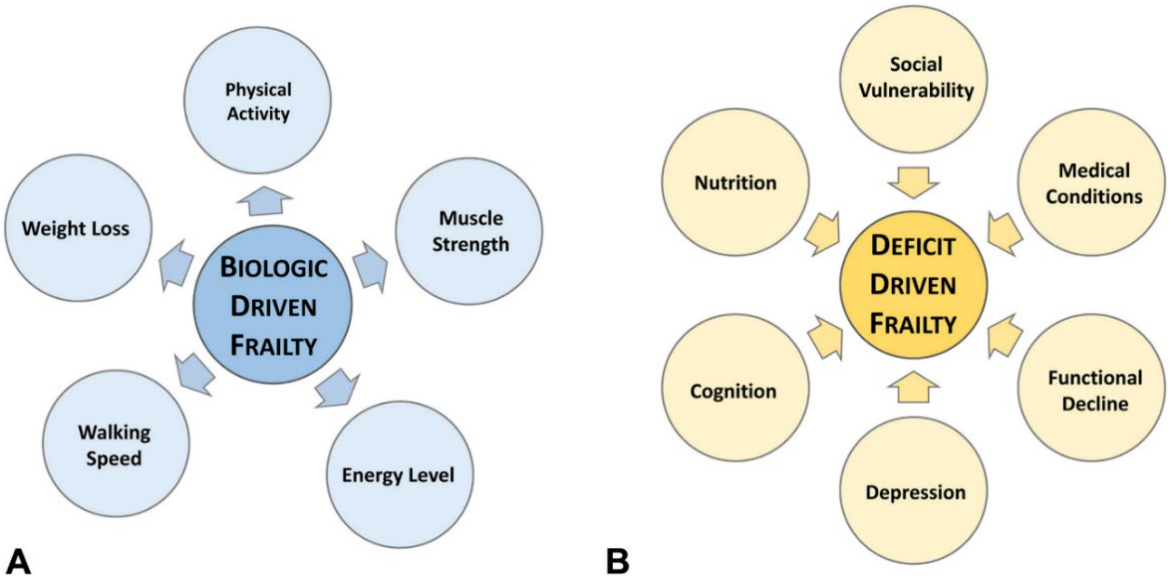

Figure 1-3 Two conceptualisations of frailty.

Key: (A) Biologic frailty definition; (B) Deficit driven frailty. Image from Robinson et al. (39) (p.1085), reused with permission from Elsevier (license 4958430070632, Nov 29, 2020).

1.5 Frailty syndrome in people living with heart failure

Frailty has become a high-priority research theme in cardiovascular medicine, particularly in people with heart failure. Frailty is highly prevalent in people living with heart failure and is an independent predictor of worse outcomes, such as hospitalisation, non-adherence to guideline-based therapy and death (40-44). A meta-analysis of studies that assessed frailty in those with chronic heart failure reported that being assessed as frail is associated with a 1.5-fold increased hazard for death and hospitalisation than being assessed as non-frail (20). Due to the advanced aged and increasingly complex chronicity of cardiovascular patients and the high number of cardiac device/surgical procedures often required, the need to isolate and manage comorbid conditions, such as frailty, has been acknowledged (23, 25). Accordingly, the assessment of frailty in people living with heart failure has been suggested as a useful risk stratification tool (45) and has generated awareness of the essential predictive role frailty assessment can have (46). A recent review article (2019) highlights this role by stating:

> *Frailty has an important prognostic role in patients with heart failure, as [it] can exacerbate the progression of heart failure as well as the occurrence of negative*

outcomes such as mortality, lower probability of surviving more than 10 years, and increased health care use (higher risk of hospitalisation, prolonged recovery, institutionalisation, etc.). Therefore, the identification of frailty is of utmost importance in patients with heart failure. Recognising those heart failure patients who are not only frail but also at risk of frailty ('pre-frail'), may allow an early and immediate multidisciplinary therapeutic intervention with the aim to improve their prognosis, outcomes, and management (47) (p. L14).

1.5.1 Frailty prevalence in people living with heart failure

Reported rates of frailty in people with heart failure vary from 15-74% (48). A recent study (2020) of patients with HF-REF (n= 8383) found that 63% were frail (49). The prevalence of frailty and heart failure increases with age (21). Furthermore, frail older adults are also at greater risk of new-onset heart failure than their non-frail counterparts (28, 50, 51). Frailty is more prevalent in women living with heart failure and in those with worse heart failure symptoms, i.e., NYHA class III-IV and congestion (49). However, a meta-analysis of frailty prevalence in heart failure patients (2017) found no significant relationship between age, NHYA class and frailty prevalence, suggesting that frailty prevalence is not determined by age or NYHA functional class but is more likely a result of other pathophysiological mechanisms (52).

1.5.2 Mechanistic links between frailty and heart failure

Frailty and heart failure share common underlying pathophysiological mechanisms, with both syndromes associated with higher levels of circulating inflammatory cytokines, sarcopenia, and dysregulation in metabolic, neuro-hormonal, and immunologic pathways (28, 47, 53). Sarcopenia and cachexia are muscle wastage conditions closely associated with frailty. They may also be potential drivers of frailty in people living with heart failure, particularly those in the advanced stages (9, 54-57). Frailty, sarcopenia, and cachexia cause unwanted weight loss, leading to extreme weakness and death (55, 57, 58). Cachexia is considered a complex metabolic syndrome associated with underlying disease and manifests as excessive weight loss and disproportionate muscle wasting (59). Heart failure and frailty also exhibit similar symptoms, such as exhaustion and decreased exercise tolerance (54). The overlapping symptomology of heart failure and frailty syndrome could make identifying underlying frailty even more difficult, as the symptoms may be wrongly

assumed to be heart failure-related deterioration (60). Cognitive impairment, depression, multimorbidity, malnutrition, reduced quality of life, and poor social support are commonly associated with frailty and heart failure syndromes (54, 61, 62).

1.5.3 Assessing frailty in people living with heart failure

A formalised assessment of frailty (i.e., using a formal/structured frailty instrument to assess frailty) in people living with heart failure is recommended by various international cardiovascular societies, namely: The European Society of Cardiology; The International Society of Heart and Lung Transplantation; The Heart Failure Society of America; the Canadian Society of Heart Failure; and the NHFA/CSANZ (4, 9, 63-65). However, a general lack of consensus regarding the definition of frailty and optimal means of assessment for use in people living with heart failure has enabled the use of subjective estimates of frailty (e.g., the *'eye-ball'* or *'end-of-the-bed'* test) in the clinical setting (25, 60, 66). In fact, in some settings, such as cardiac surgery and heart transplant centres, the *'eye-ball'* test is regularly used in place of formal frailty assessment (17, 67). Subjective estimation of frailty is potentially unreliable and may cause misclassification of frailty status, resulting in significant negative health repercussions and legal ramifications if treatment is delayed or conversely if the advancement of inappropriate treatment occurs (66).

The Frailty Phenotype (24) was recently identified as the most commonly used and highly cited instrument in the literature (35), yet there is no expert consensus or robust evidence available to confirm if this is the most suitable assessment approach for people with heart failure (45, 48). Using a 'physical frailty instrument', such as the Frailty Phenotype, which focuses on assessing only physical domains, including walking speed or weight loss, may not be reliable or clinically relevant for use in people living with heart failure. Those with heart failure often experience physical limitations and symptom exacerbations, i.e., shortness of breath and decreased exercise tolerance, which could affect their ability to perform physical tests (17, 21, 54). A 'multi-domain approach' that comprises the assessment of multiple frailty domains (rather than focusing solely on physical domains) may be more suitable for a heart failure population and presents a key area for future research (54, 62).

The high prevalence and prognostic value of frailty in people living with heart failure have been established. However, there is a lack of consensus regarding the definition of frailty

and the 'optimal' instrument for use in this population. To enable a better understanding of frailty assessment in the context of heart failure and the clinical implications of using different frailty instruments in this population, further research is needed.

1.6 Doctoral project

1.6.1 Aim

The **FRAilty MEasurement in Heart Failure (FRAME-HF) Project** aims to determine the most suitable and clinically relevant frailty instrument(s) for use in adults living with heart failure.

1.6.2 Project rationale

There is an urgent need to provide robust evidence and guidance for cardiovascular clinicians wanting to undertake frailty assessment in people living with heart failure. This project will help bridge this gap by providing pragmatic results that can assist these clinicians in successfully implementing routine frailty assessment in the heart failure clinical setting and will ultimately improve the health outcomes of frail individuals living with heart failure.

1.6.3 Research questions

This mixed methods project has been configured to answer the following research questions:

1. How is frailty measured in adults with heart failure, and what domains of frailty are most frequently assessed? (Study 1);
2. How reliable are clinician estimates of frailty compared to formal frailty assessment in determining the frailty status of adults living with heart failure? (Study 2);
3. What are the validity of frailty instruments potentially relevant for use in adults living with heart failure (Study 3); and
4. Which frailty instrument/(s) is the most suitable and clinically relevant for use in adults living with heart failure? (Data integration and meta-inferences).

1.6.4 Setting

This doctoral project was undertaken at St Vincent's Hospital, Sydney, Australia. This quaternary hospital is a global clinical and research leader in cardiovascular care and a specialist heart failure referral and transplantation centre.

1.6.5 Participants

This project involved two cohorts of participants: 1) *Individuals aged 18 years and older with a confirmed diagnosis of heart failur*e; and 2) *Cardiovascular clinicians* (i.e., registered nurses, physicians, and allied health professionals) providing treatment to people living with heart failure who attended the outpatient heart failure clinic or who were admitted to the inpatient cardiology ward during the Project. This project was undertaken over three years, from August 2016 to February 2019.

1.6.6 Overview of the thesis

The FRAME-HF project uses a deductive sequential mixed methods design to explore frailty assessment complexities in people living with heart failure. During this project, the performance of several frailty assessment methods were compared to determine which is the most suitable and clinically relevant for a heart failure population. The FRAME-HF Project consists of three discrete, yet interrelated, studies: a systematic review (Study 1), a cross-sectional study (Study 2), and a prospective cohort study (Study 3); and data integration which occurs at the conclusion of the project.

Study 1: Systematic review

A systematic review was conducted that examined how frailty was being assessed in people living with heart failure and elucidated which frailty instrument was most commonly used. This study was published in the *European Journal of Cardiovascular Nursing* and is presented in Chapter 2 of this thesis.

Study 2: Cross-sectional analysis of clinician estimates of frailty compared to formal frailty assessment in adults living with heart failure

This cross-sectional analysis focused on differentiating between subjective clinician-estimated frailty compared to conducting a formal frailty assessment in adults living with heart failure. The results of this study have been submitted to *Heart, Lung and Circulation* (currently under review) and are presented in Chapter 4 of this thesis.

Study 3: Prospective cohort study evaluating the validity of frailty instruments potentially relevant for use in adults living with heart failure

This prospective study comprised two parts; Part A compared the discriminant and convergent validity of three physical frailty instruments: the Frailty Phenotype; the Survey of

Health Ageing and Retirement in Europe Frailty Instrument (SHARE-FI); and the St Vincent's Frailty Instrument. Part B then compared the predictive ability of six frailty instruments, the three physical instruments above, along with three multi-domain instruments: the St Vincent's Frailty Instrument plus cognition and mood domains; the Deficit Accumulation Index; and the Fatigue, Resistance, Ambulation, Illnesses and Loss of weight (FRAIL) scale, to predict composite rehospitalisation and mortality at 12 months post initial frailty assessment. The results of this study have been disseminated across two manuscripts: Part A was published in the *European Journal of Cardiovascular Nursing* in 2019, and Part B is submitted to *the International Journal of Nursing Studies* and is currently under review. These results are presented in Chapter 5 of this thesis.

Data integration and meta-inference

The findings of the three FRAME-HF studies were integrated to answer the final research question and generate a series of clinical recommendations that can be used to inform future practice and assist with the implementation of routine frailty assessment in the heart failure clinical setting. These findings are presented in Chapter 6 of this thesis.

1.6.7 Thesis structure

This thesis consists of an introduction, a published systematic review of the frailty assessment instruments used in adults living with heart failure (Study 1), a methods chapter, a cross-sectional study of subjective estimates of frailty compared to formal frailty assessment (Study 2), a two-part prospective study of the validity of frailty instruments potentially relevant for use in adults living with heart failure (Study 3), and finally, the data integration, future directions and conclusion chapter (Refer Figure 1.4).

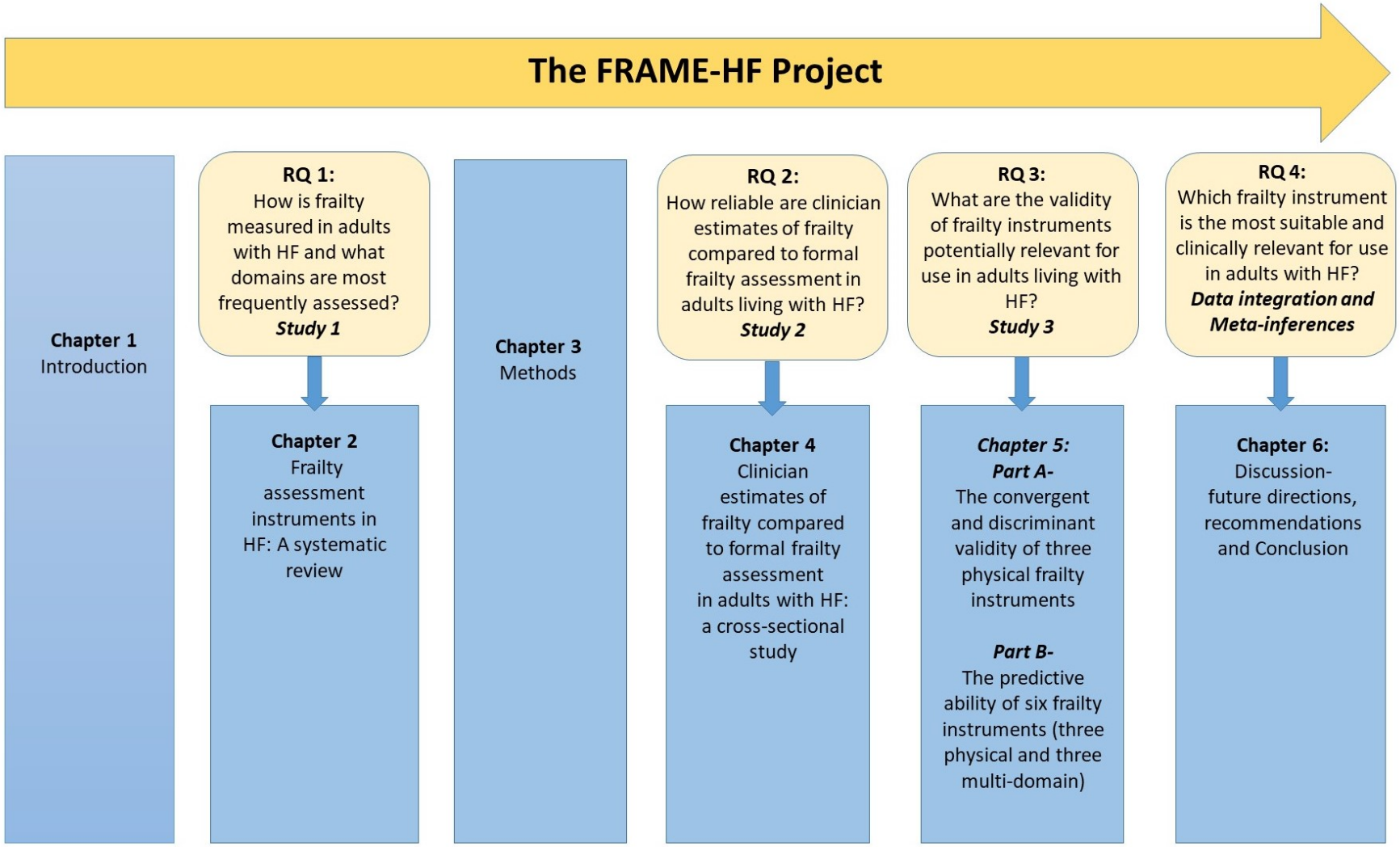

Figure 1-4 Structure of thesis.

1.7 Conclusion

This chapter provided an overview of frailty syndrome in the context of heart failure. It highlighted that further research into the optimal means of frailty assessment in people with heart failure is required. The doctoral projects aim, research questions and thesis structure were also introduced. The following chapter will present the results of the FRAME-HF systematic review, which explores how frailty is being assessed in people with heart failure; this will help set the context for the forthcoming studies of the FRAME-HF project.

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Chapter 2: Frailty assessment instruments in heart failure: a systematic review

2.1 Preamble

Interest in assessing frailty in people living with heart failure has grown exponentially over the last decade, with numerous research studies reporting the clinical implications of frailty in heart failure published, including several review articles. However, a review article that specifically focused on the frailty assessment instruments used in heart failure studies was lacking. This chapter presents the results of a systematic review of the frailty assessment instruments used in heart failure research and highlights the frailty domains most frequently assessed. This systematic review provides an important contextual overview and foundation for the forthcoming chapters of this thesis and justifies the importance of defining the most suitable frailty assessment method for the heart failure population. This study was published in *the European Journal of Cardiovascular Nursing,* as referenced below.

2.2 Publication reference for Study 1

This chapter presents a slightly modified version of the original manuscript. The published version is provided in Appendix 1.

> **McDonagh J**, Martin M, Ferguson C, Jha SR, Macdonald PS, Davidson PM, Newton PJ, Frailty assessment instruments in heart failure: A systematic review. European Journal of Cardiovascular Nursing. 2018;17(1): 23–35.
> [Impact factor 2.296] Citations: 49

2.3 Systematic review abstract

Background: Frailty is an independent predictor of mortality across many conditions. Reported rates of frailty in heart failure range from 15-74%. There are several instruments available to assess frailty; however, there has been no consensus on the most appropriate instrument for use in individuals with heart failure to date.

Aims: To identify how frailty is assessed in individuals with heart failure and elucidate which frailty domains are most frequently assessed.

Methods: Key electronic databases (Medline, Cochrane Central and CINAHL) were searched to identify studies that assessed frailty in individuals with heart failure using a formal frailty instrument.

Results: Twenty studies drawn from twenty-four articles were included, from which a total of seven different frailty instruments were identified. The most commonly used instrument was Fried's Frailty Phenotype (n= 11), with most studies using a modified version of the Fried Phenotype (n= 8). The second most commonly used instrument identified was the Comprehensive Geriatric Assessment (n= 4).

Conclusion: There is an increasing interest in assessing frailty, but to date, there is no frailty instrument validated specifically in the heart failure population. Further research is needed to gain consensus on the most appropriate time-point for assessment and explore the impact that disease-related deconditioning and/or progression of heart failure symptoms may have on frailty assessment.

Key words: frailty, heart failure, frailty assessment

2.4 Introduction

Frailty is a multidimensional syndrome characterised by a state of increased vulnerability to acute stressors, such as hospitalisation, falls and infection. It is an independent predictor of mortality (1, 2) and is the most problematic expression of population ageing (3). With the growing focus on multimorbidity, this construct has increasing utility (4). Frailty is most commonly defined as meeting three out of five phenotypic criteria: low physical activity, unintentional weight loss, slow walking speed, weak grip strength, and/ or exhaustion (5).

Heart failure is a common yet complex cardiac syndrome developing due to structural or functional damage to the heart, which reduces its ability to fill with and/or pump blood effectively (6, 7). The prevalence of heart failure increases significantly with age (8) and is associated with high morbidity and mortality (9, 10). Heart failure is a leading cause of hospitalisation and general practitioner (GP) consultation, particularly in the elderly population (10).

The high prevalence of frailty in heart failure is well documented (11-13), and as such, it has been identified as an emergent area of research priority (14). The reason for this is complex and multifaceted. Some of these considerations determine prognosis and assist in the assessment of therapies, particularly those that are invasive (15). The presence of frailty can predict adverse outcomes in heart failure (12, 16, 17). However, the variability in defining frailty and the use of various measures have made it problematic to compare the prevalence of frailty and its impact on outcomes between studies.

2.5 Aims

The purpose of this review was to examine how frailty is assessed in individuals with heart failure.

The five key objectives of this review are:

I. Summarise the available instruments that have been used for frailty measurement in heart failure
II. Highlight the core domains of frailty assessments
III. Identify the strengths and limitations of the instruments
IV. Discuss implications for future heart failure clinical research and practice

2.6 Methods

Following consultation with a health librarian, key electronic health-related databases (MEDLINE and CINAHL and the COCHRANE Central) were searched from 2001- 2016. In 2001 the seminal paper defining frailty as a phenotype was published by Fried and colleagues (5); accordingly, it was selected as the start point for this review. Search terms included are listed in Table 2.1. Original studies were selected that included participants with a diagnosis of heart failure, i.e., individuals exhibiting heart failure symptoms or receiving treatment for heart failure and studies must have addressed measurement of frailty using a structured instrument with pre-defined criteria. Only original studies were included. Conference abstracts, reviews and editorials were excluded.

Firstly, articles were extracted from the electronic databases; following this, they were screened against the eligibility criteria based on title/abstract. Articles then underwent full-text review by two independent researchers (J.M and L.M), where necessary, a third researcher (P.J.N) was consulted. In the case of multiple studies drawn from the same data set, the original paper was included in the summary table. The review was conducted in accordance with the PRISMA guidelines (18).

Table 2-1 Search terms.

Database	Search terms
Medline	*Frailty*: MeSh – frail elderly, frailty as a key word, vulnerability, disability, cachexia, sarcopenia, hand grip, gait speed *Heart failure*: heart failure.mp., Ventricular dysfunction, left.sh. Cardiomyopathy.mp. Left ventricular ejection fraction.mp. *Measurement*: Measurement as key word, instrument, outcome measure, outcome assessment, hand grip
Cochrane Central and CINAHL	Frailty: frail elderly, frailty as a key word, vulnerability, disability, cachexia, sarcopenia, hand grip, gait speed Heart failure: heart Failure, ventricular dysfunction, cardiomyopathy, left ventricular ejection fraction

2.6.1 Quality assessment of included studies

Quality assessment of included studies was undertaken by two independent reviewers in accordance with the Joanna Briggs Institute (JBI) Critical Appraisal Checklist's for case-control studies, studies reporting prevalence data, cohort studies and randomised control studies outlined in the JBI Reviewers' Manual: 2014 edition (19). To the authors' knowledge, the included articles also conformed to the standards outlined in the Declaration of Helsinki (20). Due to the heterogeneity of frailty assessment among the included articles, a meta-analysis was not performed. Results are summarised in table and narrative form.

2.7 Results

The search strategy retrieved a total of 740 articles. Following the removal of duplicates, 699 were screened, with 664 excluded based on inappropriate title/abstract. The remaining 35 underwent full-text review. After consensus was gained, 24 articles were included in this review; from these 20 were identified as original studies (Refer Figure 2.1).

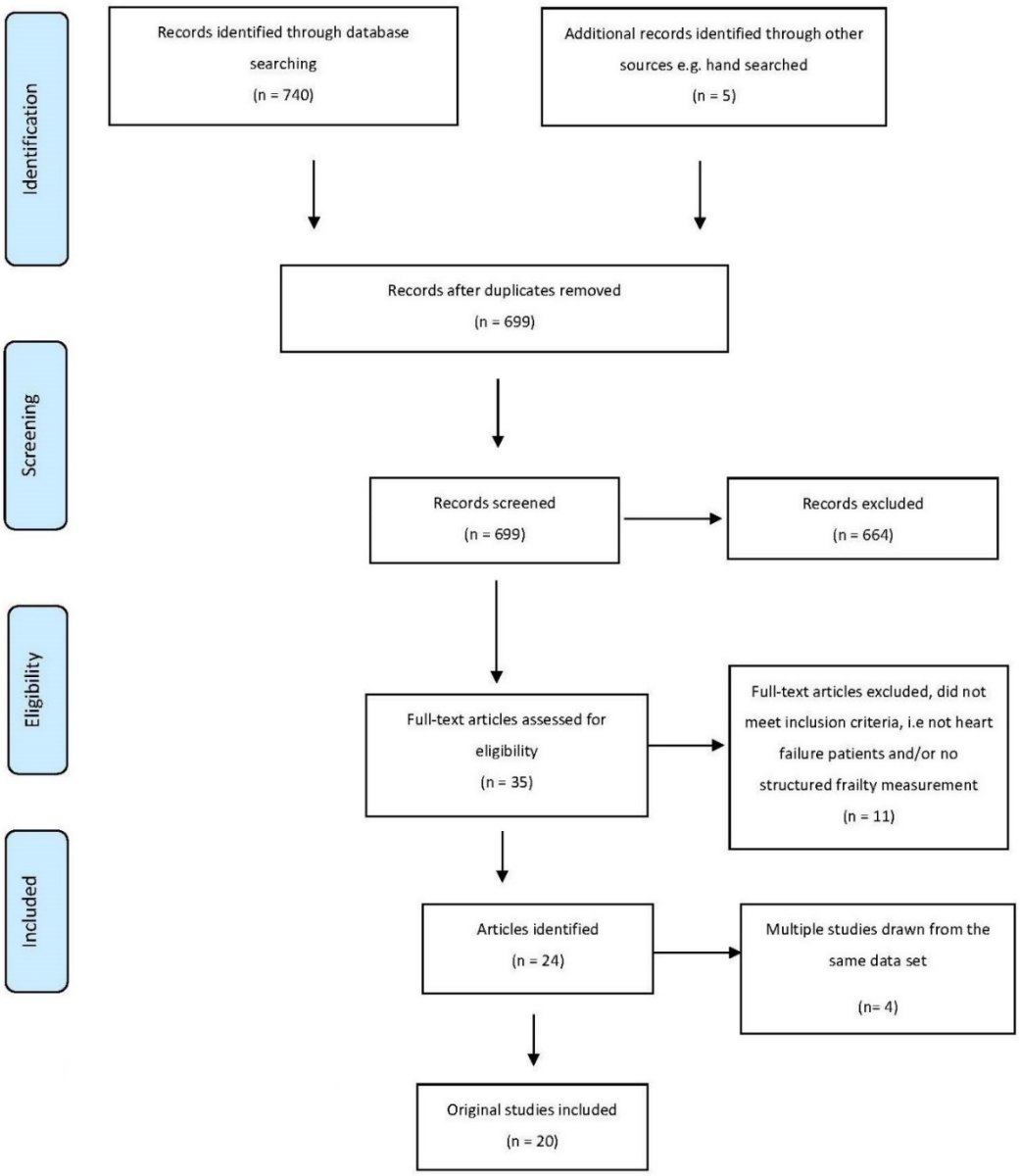

Figure 2-1 Prisma flow diagram.

Seven different frailty instruments were identified from the 20 studies. The most commonly utilised frailty instruments (n=11 [55%]) were based on the Frailty Phenotype (5); with the majority (n=8) using modified versions of Fried's original tool (21) (22) (23) (24) (25) (17) (26) with one study assessing a single-item component (27). The second most commonly utilised instrument was the Comprehensive Geriatric Assessment (CGA) (n= 4), followed by the Deficit Accumulation Index (n=3). A summary of the results from each study and the instrument utilised is provided in Table 2.2.

Table 2-2 Summary of results.

Author/Year	Topic/focus/ question	Context/setting/ sample	Methods	Frailty instrument	Frailty domains assessed	Results	JBI Critical Appraisal Score
Abou-Raya & Abou Raya (2009) (21)	Evaluate the association between osteoporosis & CHF	Convenience sample 83 consecutive patients with CHF & osteoporosis & 54 age match controls with osteoporosis and no CHF Out-patient clinic	Case control study Inflammatory markers- TNFa & IL-6 were measured	FP (modified)	Physical: Weight loss, exhaustion, walking speed & grip strength	CHF group (n = 83) age 69.9 ± 4.5 51% were female Controls (n = 54) age 70.1 ± 3.9 52% were female CHF group: Frail = 29% Pre - frail = 43 Not frail = 28% Control group: Frail = nil Pre- Frail = 46% Not Frail = 56% Higher frailty scores associated with lower Bone Mineral density scores & lower ejection fraction Levels of IL-6 & TNF-a significantly higher in CHF group compared to Control (p= 0.001 & p=0.005 respectively)	6/10
Altimir et al. (2005) (28)	To describe the degree of fragility in all patients treated in a HF clinic & to evaluate age and sex differences	Convenience sample 360 consecutive patients Outpatient HF clinic	Cross-sectional design	CGA (Barthel index, OARS scale, The Pfeiffer test, geriatric depression scale and social interview)	Physical/functional: Barthel Index of activities of daily living & OARS scale Cognitive- Pfeiffer test Psychosocial- depression & social interview	Mean age 65.2 ± 10.9 74% were female Fragility detected in 42% of patients (more prevalent in >70 years [53% vs. 33%] and in women [63% vs. 34%, p<0.001)	8/9

Author/Year	Topic/focus/ question	Context/setting/ sample	Methods	Frailty instrument	Frailty domains assessed	Results	JBI Critical Appraisal Score
						Fragility was strongly associated with anaemia (p<0.001) and diabetes (p=0.002) Abnormal Pfieffer cognitive test found in 8% of patients, more frequent in those >70yrs of age (14% vs. 3%. p=0.003) Fragility also strongly correlated with the number of hospital admissions	
Boxer, Dauser et al. (2008) (22) **(29)** **(30)**	To identify relationships between anabolic hormones, inflammatory markers and physical function	***60 patients*** aged ≥60yrs with a LVEF ≤40% Outpatient university HF program	Cross-sectional design 6MWT Hormones (testosterone, DHEAS, cortisol, vitamin D) & inflammatory markers (hsCRP & IL-6) were measured	FP (modified)	6MWT Physical: Weight loss, exhaustion, walking speed, physical activity level & grip strength	72% were male (mean age 77±9) 28% were female (mean age 78±12). 17 (28%) were not frail, 12 (20%) were positive in 1/5 FP criteria, 15 (25%) had 2/5, 16 (25%) had 3-5/5 characteristics. 48% of patients had a free testosterone level below normal 77% had DHEAS level below normal 30% had Vitamin D levels below normal Higher FP score was correlated with higher hsCRP, higher IL-6 and lower Vitamin D (all p<0.05)	7/9
Boxer & Kleppinger et al. (2010) (23)	To determine if HF contributes to the development of functional decline and frailty	Follow up from the previous study Convenience sample 20 patients	Follow-up of participants from a previous observational study	FP (modified)	6MWT Physical: Weight loss, exhaustion, walking speed, physical activity level & grip strength	There were no changes in frailty/endurance status overtime Deaths occurred in 18% of the NF/NE group	8/9

Author/Year	Topic/focus/ question	Context/setting/ sample	Methods	Frailty instrument	Frailty domains assessed	Results	JBI Critical Appraisal Score
						6MWT & frailty were each associated with mortality	
Buck & Riegel (2009) (31)	To determine if frailty explains the variability of HRQL in older adults with HF	Convenience sample 130 patients	Secondary analysis	Novel frailty instrument used	Age Comorbidities (Charlson index) Symptom severity (fatigue, dyspnoea on exertion & chest pain)	A benchmark sample of 130 adults was used to develop the frailty index, the median age of 72 years, 98% NYHA III or IV A test sample was also used; one half was to test the index, and the second half was to validate the stability of the index Frailty negatively impacts a HRQOL in older adults with HF	8/9
Cacciatore et al. (2005) (12)	To assess long term mortality in 120 subjects with CHF and 1139 without CHF	1332 participants Randomly selected Outpatients. Subjects were >65 years of age	Case-control study	Frailty staging system	Disability, mobility, cognitive function, visual function, hearing, urinary continence & social support	CHF subjects (n=120): 60% were female and older than 75 years (mean 75.9 ± 6.7) Subjects without CHF (n=1139): 56% were female and younger than 75 years (mean 74.0 ± 6.3) In the CHF group, 15% were frail Death progressively increased more with frailty in subjects with or without CHF, the probability of survival progressively decreases after 1, 6 and 12 years of follow-up	8/10
Chung et al. (2014) (27)	To establish the predictive value of handgrip strength as a marker of frailty in VAD patients	72 Patients With advanced HF	Observational cohort study	Hang grip strength	HGS measured pre VAD implant and monthly for 6 Months post	Mean age of patients 59 ± 2 71% were NYHA class IV 17 (22%) were frail 56 (78%) were not frail	8/9

Author/Year	Topic/focus/ question	Context/setting/ sample	Methods	Frailty instrument	Frailty domains assessed	Results	JBI Critical Appraisal Score
						Low HGS correlated with low albumin levels Baseline HGS was lower in patients who died post-VAD implant HGS < 25% of total body weight (BW) distinguished patients with a greater likelihood of early postoperative mortality (sensitivity 72% & specificity 80%) Patients with HGS <25% of BW were found to have significantly higher rates of bleeding postoperatively (54 vs. 17%, p= 0.002), higher infections rates were also found (85 vs. 54%, p=0.012)	
Dominguez-Rodriguez et al. (2015) (32)	To assess the impact frailty status has on post-implantation outcomes after CRT-D	102 patients With non-ischemic cardiomyopathy aged >70 years & scheduled to undergo CRT-D	Prospective cohort study	FP	Physical: Weight loss, exhaustion, walking speed, physical activity level & grip strength Barthel index also collected as an additional measure	Mean age 73 ± 3 years 53% were male All patients had an EF of <30% and were in NYHA class III or IV 73 (72%) patients were Non-frail 29 (28%) patients were Frail Frail patients had significantly higher rates of dyslipidemia (66% vs. 41%, p= 0.026) No significant difference in hospital stay between frail & non-frail A higher number of frail patients experienced decompensated HF after CRT-D implantation than non-	9/11

Author/Year	Topic/focus/ question	Context/setting/ sample	Methods	Frailty instrument	Frailty domains assessed	Results	JBI Critical Appraisal Score
						frail patients (51.7% vs. 16.4%, p= < 0.001)	
Dunlay et al. (2014) (33)	Assess the post-operative outcomes associated with frailty in patients undergoing LVAD implantation as DT.	99 patients All patients undergoing LVAD as DT were eligible for inclusion	Observational study	Deficit Accumulation index	Index based on 31 deficits related to: Self-care and activities of daily living, medical conditions and comorbidities & depression	Mean age of cohort 65.1 ± 9.4 years 82% were male Mean EF 18.5% ± 6.8 62% of patients had a prior myocardial infarction & 37% had diabetes Of the 99 patients: Not frail = 32% Intermediate frail = 33% Frail = 34% 1 year mortality rates were 16.2%, 21.2% & 39.9% (p= 0.007) for not-frail, intermediate frail & frail respectively	8/9
Ferguson et al. (2016) (24)	To describe the clinical characteristics of patients admitted to hospital with Chronic HF and concomitant atrial fibrillation and to document the rate/type of anticoagulant	Convenience sample Inpatients admitted to the cardiology ward 137 patients	Prospective observational study	SHARE Frailty index (modified FP)	Five physical domains of frailty: Appetite, exhaustion, walking speed, physical activity level & grip strength	92 patients were assessed for frailty 63% of patients were classified as frail Being frail and having higher comorbidity was associated with not receiving anticoagulant drugs at discharge	8/9
Gastelurrutia, Lupon, Altimir et al. (2013) (34) (35)	Assess the relationship between fragility and QoL perceptions in outpatients with HF	Convenience sample 1405 consecutive patients 1314 consecutive patients (35)	Observational study	CGA	Physical/functional: Barthel Index of activities of daily living & OARS scale Cognitive- Pfeiffer test	Mean age 66.7 ± 12.4 72% were male 52.8% had coronary heart disease 60.9% had hypertension 54.5% had renal failure	8/9

Author/Year	Topic/focus/ question	Context/setting/ sample	Methods	Frailty instrument	Frailty domains assessed	Results	JBI Critical Appraisal Score
		Outpatients presenting to a HF clinic with at least 1 HF hospitalisation &/or reduced EF <40%			Psychosocial- depression & social interview QoL measure- Minnesota living with HF questionnaire Patients were considered fragile if they had one abnormal evaluation identified	44% were considered frail The mean QoL score was 39.0 ± 18.9 for frail patients and 25.3 ± 17.1 for non-frail patients ($p < 0.001$)	
Jha et al. (2016) (25)	To determine the prevalence of frailty in patients referred for heart transplantation	Convenience sample 120 consecutive patients Advance HF patients with NYHA class III or IV referred or waiting for heart transplantation Hospital inpatients and outpatients are seen in the HF clinic	Observational study	FP (modified)	Five physical domains: Appetite, exhaustion, walking speed, physical activity level & grip strength Cognitive and depression screening was also undertaken	Mean age 53 ± 12 69% were male 81 patients (68%) were non-frail 39 patients (33%) were classed as frail There was a significant difference in overall survival, with more deaths occurring in the frail group ($p< 0.005$)	7/10
Lupon et al. (2008) (16)	To determine the impact of frailty and depressive symptoms on the 1-year mortality rate and rate of hospitalization for HF during a 1 year F/U period	622 participants Outpatient HF unit All patients referred to the HF unit, no exclusion criteria	Observational study Scheduled visits by a nurse every 3 months and doctor visits every 6 months	CGA	Physical/functional: Barthel Index of activities of daily living & OARS scale Cognitive- Pfeiffer test Psychosocial- depression & social interview	73% were male, and ≥70 years (55%) median age 68 (29-93). Fragility was detected in 40% of participants and depressive symptoms in 25% of participants (61% were female, 53% were ≥70 years) 1 year F/U: 60 participants (10%) had died & 101 (17%) had HF hospitalizations	8/9

Author/Year	Topic/focus/ question	Context/setting/ sample	Methods	Frailty instrument	Frailty domains assessed	Results	JBI Critical Appraisal Score
						The presence of fragility was strongly associated with increased 1-year mortality (17% vs 5% without fragility; p<0.001) Higher mortality in frail patients was observed in ≥70yrs (20% vs 8%; p=0.003) and in younger patients (13% vs 3%; p=0.001) The presence of fragility was also associated with increased HF hospitalization (21% vs 13%, p=0.01)	
Madan, Fida, Barman et al. (2016) (17)	To investigate the utility of frailty assessment in advanced HF	40 consecutive patients Outpatients that presented to a HF clinic	Single-centre pilot study	FP (modified) 6MWT	Five domains: Weight loss, exhaustion, walking speed, physical activity & grip strength	58% were female Mean age was 74.9 ± 6.5 No subjects were not frail Pre-frail: 14 participants (35%) Frail: 26 participants (65%) Compared to the pre-frail group, frail participants were at a 2-fold increased risk of all-cause hospitalisation or death (HR 1.93, 95% CI 1.15-3.25, p=0.013), after adjusting for other factors (i.e. Race, age, sex, diabetes & Charlson index) it remained significant (p=0.031) There were more all-cause hospitalisations in the frail vs. pre-frail group (p= 0.017) Frailty was associated with an increased risk of non-HF-related hospitalisations (p= 0.028) but not HF-related hospitalisations	7/9

Author/Year	Topic/focus/ question	Context/setting/ sample	Methods	Frailty instrument	Frailty domains assessed	Results	JBI Critical Appraisal Score
						The 6MWT was not predictive of either of the primary endpoints in this cohort & there was no correlation between the 6MWT & frailty	
McNallan, Singh et al. (2013) (36) (11)	To determine the prevalence of frailty in a community cohort of patients with HF and to determine if frailty increases health care utilization	448 patients Outpatients Sub-study of 223 patients	Observational study Mean F/U was 2 ± 1 years Health care utilisation included hospital admission, outpatient visits and ED visits	FP (FP, Deficit Accumulation index compared in sub-study)	Five domains: Weight loss, exhaustion, walking speed, physical activity & grip strength	57% were male Mean age of the cohort was 73 ± 13 years Of 332 patients, 74% had some degree of frailty (19% frail, 55% intermediate frail). In the frail group, 54% were male, and 58% were male in the intermediate frail group Over mean F/U period of 2 ± 1 yrs 20,164 outpatient visits, 1440 ED visits and 1057 hospitalizations occurred. After being adjusted for potential confounders, frailty was associated with a 92% increased risk for ED visits and a 65% increase for hospitalizations Frailty is a strong independent predictor of ED visits and hospitalisations In the sub-study (11), the FP and DAI were correlated, and both equally predicted mortality	8/9
Mlynarska et al. (2016) (37)	To establish the degree of frailty in patients with advanced HF receiving CRT	**106 patients** who qualified for CRT were included	Prospective cohort study	Canadian health and ageing clinical frailty scale (CSHA-CFS)	Clinician rated frailty rating scale- Domains: physical activity level, disability/dependence on	Frailty syndrome was found in: 82% of de novo patients & 69% of upgrade patients 78% of the total cohort were frail	8/9

Author/Year	Topic/focus/ question	Context/setting/ sample	Methods	Frailty instrument	Frailty domains assessed	Results	JBI Critical Appraisal Score
		Retrospectively divided into groups- de novo CRT- 74 patients & Upgrade to CRT- 32 patients			others, comorbidity, activity level,	The average values of the CSHA-CFS were statistically higher in the de novo group when compared to the upgrade group (p= 0.027) Women in the de novo group had significantly higher values of frailty on the CSHA-CFS when compared to women in the upgrade group (p= 0.048) Diabetes & arterial disease were found to have a significant effect on frailty	
Newton et al. (2016) (26)	To provide an insight into the acute HF admissions in New South Wales W & the Australian Capital Territory	Convenience sample 811 patients Hospital inpatients that were admitted to 24 participating hospitals within one month	Prospective audit	SHARE Frailty index (modified FP)	Five physical domains of frailty: Appetite, exhaustion, walking speed, physical activity level & grip strength	58% were male Mean age 77 ± 13 557 patients underwent a frailty assessment, 71% were classified as frail 21% were classified as pre-frail 77% of frail participants were classed as HF with preserved ejection fraction	8/9
Pulignano et al. (2010) (38)	To determine which patient's benefit mostly from DMP, according to their frailty profile	173 consecutive patients Aged ≥70yrs Outpatient clinics Normal or reduce LVEF NYHA III or IV Requiring IV inotropes/vasodilator and/or diuretic	RCT conducted at two HF clinics. Participants were randomly assigned to either a multidisciplinary DMP or usual care A modified frailty score of range 1-6 was used as an index of global function impairment	CGA	Physical/functional: Barthel Index of activities of daily living & OARS scale Cognitive- Pfeiffer test Psychosocial- depression & social interview	173 patients were randomized to DMP, and 87 were usual care 136 (79%) of the total cohort were frail 37 (21%) were not frail Mild to moderate frailty (score 2-3) was associated with significant improvement of outcomes (death and/or HF admission and all-cause admission) in the DMP group than in the usual care.	8/13

Author/Year	Topic/focus/ question	Context/setting/ sample	Methods	Frailty instrument	Frailty domains assessed	Results	JBI Critical Appraisal Score
						Even in the more frail patients (score 4-6), a reduction in HF admissions was observed The DMP intervention was more cost-effective in moderately frail patients than usual care. There was no difference in the non-frail or severely frail groups	
Vidan et al. (2014) (39)	To evaluate clinical outcomes (death & rehosp), functional evolution, QoL and use of social resources at 1, 3, 6 & 12 months after admission in elderly patients hospitalised for HF	Convenience sample 450 patients Consecutive elderly patients hospitalized for HF	A prospective observational cohort study 1 year follow up (phone interviews at 1,3,6, & 12 months)	FP		49.6% were female The mean age of the cohort was 80 ± 6 69.1% were recruited from the cardiology ward (17.3% internal medicine and 13.6% geriatric ward). 70% total were classified as Frail at index admission (67.4% of cardiology cohort, 73.1% of internal med & 80.3% of geriatric). No outcome data regarding death/rehospitalisation reported.	8/9
Uchmanowicz, Wleklik & Gobbens (2015) (40)	To evaluate the correlation between frailty and self-care abilities in HF patients	110 patients Hospitalised with chronic HF in a cardiology ward	Observational study over 12 months	Tilburg Frailty Indicator	It consists of two parts: Socio-demographic characteristics & potential determinants of frailty collected by clinicians 15 self-reported questions dived into three domains- physical, psychological & social	54% were male The mean age of the cohort was 66 ± 11 83 (76%) of patients were frail 27 (25%) were not-frail Correlation analyses show that total frailty and each of its components (physical, psychological, social) increase with age, duration of illness and NYHA class	8/9

Author/Year	Topic/focus/ question	Context/setting/ sample	Methods	Frailty instrument	Frailty domains assessed	Results	JBI Critical Appraisal Score
					Total score ranges from 0 to 15; the higher the score, the higher the frailty, Frailty diagnosed if the score is >5	Longer duration of HF was correlated with increased frailty Only social components of the TFI were associated with the ability to self-care in this cohort	

Key: *Chronic heart failure* -**CHF**, *Tumor Necrosis factor alpha* -**TNFa**, *Interleukin 6* – **IL-6**, *Frailty Phenotype* – **FP**, *Comprehensive Geriatric Assessment* – **CGA**, *Older Americans Resource & services* – **OARS**, *Left ventricular ejection fraction* – **LVEF**, *Dehydroepi-androsterone sulphate* – **DHEAS**, *High sensitivity C-reactive* protein – **hsCRP**, *Six Minute Walk Test* – **6MWT**, *Health-Related Quality of Life* – **HRQL**, *Left Ventricular Assist Device* – **LVAD**, *Hand Grip Strength* – ***HGS***, *Cardiac Resynchronisation Therapy Defibrillator* – **CRT-D**, Deficit Accumulation Index – DAI, *Quality of Life* – **QoL**, *Cardiac resynchronization therapy* – **CRT**, *Disease management Program* – **DMP**, *Canadian health and ageing clinical frailty* scale - **CSHA-CFS,** *Tilburg Frailty indicator* - **TFI**

2.8 Discussion

The FRAME-HF systematic review identified a diverse range of frailty assessment instruments to assess frailty in adults living with heart failure. Several important concepts were uncovered, which help inform the latter stages of this doctoral project. (Refer Figure 2.2).

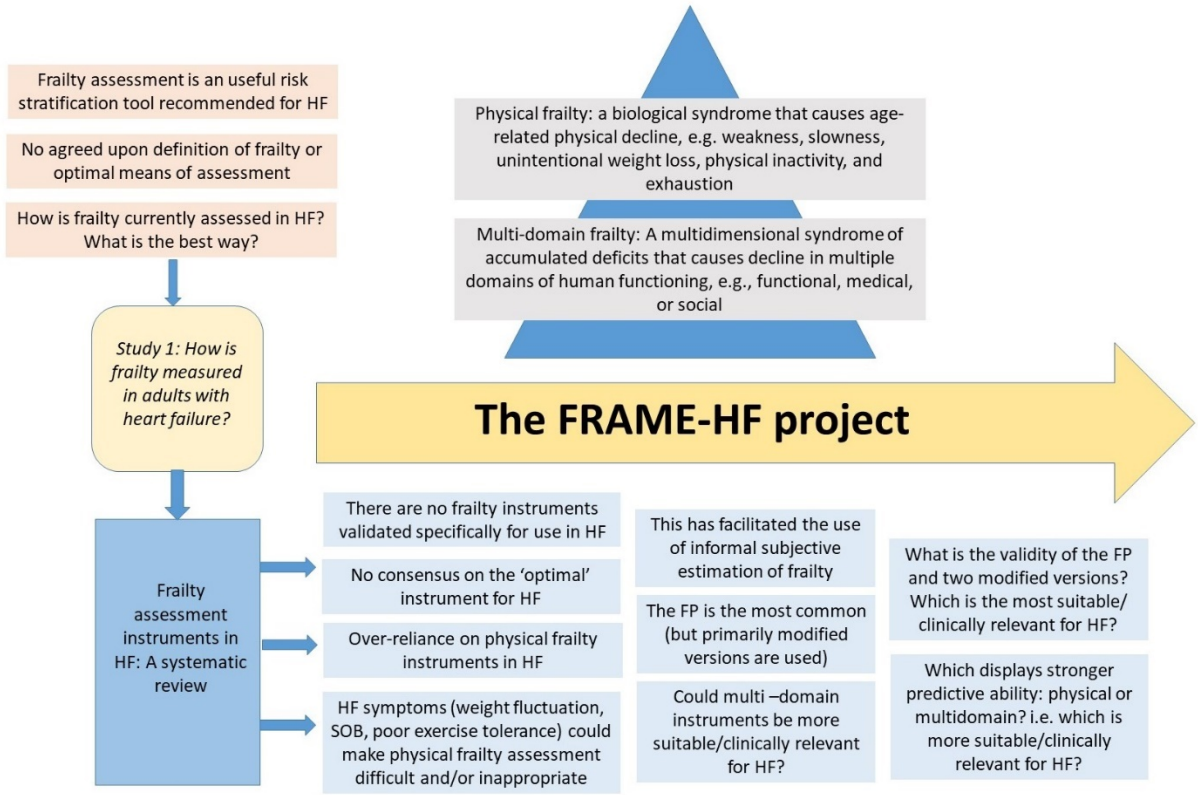

Figure 2-2 Concepts emerging from the systematic review.

The individual frailty instruments identified in this review are discussed in further detail below.

The Frailty Phenotype

The Frailty Phenotype defines frailty as a biological syndrome that causes age-related physical decline. This scale focuses on five physical domains of frailty: exhaustion, physical inactivity, walking speed, grip strength, & weight loss (41) and was first developed as part of the Cardiovascular Health Study (42). The Frailty Phenotype has become one of the most well-known definitions and is consistently identified as the most commonly used measure throughout the literature (43). Whilst it has been used in numerous heart failure studies, the definition was initially validated in community-dwelling older adults. The Frailty

Phenotype consists of a series to be performed by a clinician. These include measurement of handgrip strength as assessed by a dynamometer and a five-meter gait speed test alongside self-reported measures regarding weight loss, exercise tolerance and physical activity.

Whilst the Frailty Phenotype is the most commonly used instrument, it is unclear whether all five domains of the Frailty Phenotype are necessary or whether a single measure is equally effective (44, 45). Reduced handgrip strength and five-metre gait speed have been recommended as predictive single-item measures of frailty (1). Frailty instruments that measure multiple domains are often time-consuming to complete and, as such, may not be feasible in a time-constrained, acute clinical environment. Therefore, the use of a single-item measure may be more appropriate. Using handgrip strength as a measure of frailty in a cohort of individuals with heart failure undergoing ventricular assist device (VAD) implantation demonstrated that individuals with reduced handgrip strength pre-VAD implant had higher rates of post-operative complications and lower survival rates. The use of handgrip strength was favoured over a full functional assessment in this cohort due to their minimal tolerance to undertake physical exertion and their disease-related deconditioning, which is common in heart failure patients (27). A limitation of handgrip strength as a single measure is that there may be certain individuals who are unable to perform a handgrip strength measurement, such as those with hemiplegia, individuals unable to follow commands due to advanced dementia or other cognitive illness, those post sternotomy or permanent pacemaker insertion and individuals with altered level of consciousness.

Modified Frailty Phenotype

Several studies included in this review used a form of modified Frailty Phenotype (21, 22, 25), all the versions of the Frailty Phenotype used in these studies have variations to the original Fried Phenotype, such as using self-reported measures of appetite in place of weight loss (25) or altering the distance of the walk speed test (21). These modified versions of the Frailty Phenotype have not been validated for routine use in heart failure.

The SHARE Frailty Index (modified Frailty Phenotype)

The SHARE frailty index (SHARE-FI) was developed as part of the Survey of Health Ageing & Retirement in Europe (46) and consists of variables relating to the five domains of the Frailty Phenotype. It was designed to offer a valid alternative to the Frailty Phenotype in the

European context and aimed to facilitate the rapid assessment of frailty in the primary care setting (47). It was validated in a cohort of community-dwelling adults and provided a gender-specific frailty class. It is relatively similar to the Frailty Phenotype, except for weight loss and slowness. The 'weight loss' criteria being replaced with self-reported measures related to appetite and the 'slowness' component assessed using questions regarding functional limitation rather than the 5-meter gait speed test (5, 47). The SHARE-FI has been piloted in various clinical settings (48) but has only had minimal use in heart failure (24, 26) and is currently not validated for routine use in this group.

The Comprehensive Geriatric Assessment

The Comprehensive Geriatric Assessment (CGA) was first developed by Marjory Warren in the 1930s (49, 50) as a method of structured assessment of an older person's psychosocial, medical, functional and environmental needs in an attempt to improve their treatment and follow-up plans (51). The modern CGA involves the use of previously validated geriatric scales, i.e., The Barthel Index of activities of daily living (52), The older Americans Resource and services (OARS) scale (53), The Pheiffer cognitive test (54) and the Yesavage geriatric depression scale (55) The use of the CGA is highly cited in the literature, particularly, in the cancer care specialty (56-58).

The CGA has been validated for use as a frailty measurement tool in the general geriatric population (59) and has consistently demonstrated reliability for measuring frailty in various heart failure populations (16, 28, 34). It provides a multidimensional team approach to measure functional, social and cognitive domains of frailty (13), including disability and comorbidities, which have otherwise been acknowledged as related yet independent syndromes. The CGA and the Frailty Phenotype both include self-reported patient questions and multiple assessments and, as such, may be considered too time-intensive for routine use in the clinical setting.

Deficit Accumulation Index

The Deficit Accumulation Index (also known as the Frailty Index) conceptualises frailty as an accumulation of deficits. The Deficit Accumulation Index (60) was developed using data from the Canadian Study of Health and Ageing (61) and includes the assessment of multiple variables, including: 1) self-care ability; 2) dependence on assistive devices; 3) medical conditions; 4) body mass index and; 5) depression. It is designed so that many of the

variables can be extracted from the patient medical records; therefore, the Deficit Accumulation Index may be more appropriate for the time-poor clinician. The benefit of the Deficit Accumulation Index over the Frailty Phenotype is that it assesses various domains of human functioning instead of only physical domains. In the context of heart failure, the Deficit Accumulation Index has been used in preoperative adults (mean age 65 years) undergoing left ventricular assist device (VAD) implantation as destination therapy (33) and in a cohort of community-dwelling older adults (mean age 71 years) (11) with a combined total of 222 patients. The Deficit Accumulation Index demonstrated a correlation with the Frailty Phenotype and was equally able to predict mortality (11) in a heart failure population. It is yet to be formally validated for use in heart failure.

Tilburg Frailty indicator

The Tilburg Frailty Indicator (TFI) is based on a definition that frailty is a consequence of a combination of life-course determinants and diseases leading to a decline in various domains of physical, psychological and social functioning which ultimately causes adverse outcomes such as disability, health care utilization and death (62). The TFI consists of two parts; the first is comprised of variables related to the socio-demographic characteristics of the participant, and the second comprises 15 self-reported questions divided into physical, psychological and social domains (40). The TFI has previously demonstrated validity and reliability in a cohort of 484 community-dwelling persons aged 75 years and older (62). It has not yet been validated for use in a heart failure population.

Frailty Staging System

The Frailty Staging System (FSS) was modified from a previous examination method used to assess elderly patients for functional disability (63), it shortens the original fifteen target areas down to seven core domains of functioning: disability, mobility, cognitive function, visual function, hearing function, urinary continence and social support (12). The FSS has not been validated in a heart failure population.

Canadian Study of Health and Ageing Clinical Frailty Scale

The Canadian Study of Health and Ageing Clinical Frailty Scale (CSHA-CFS) is a seven-point frailty scale that was applied to individuals aged greater than 65 years (n= 2305) who participated in the second stage of the Canadian Study of Health and Ageing (61, 64). CSHA-

CFS is a frailty rating score and ranges from *'Very Fit'* to *'Severely Frail'.* Whilst the CSHA-CFA was able to provide predictive information regarding mortality or the need for institutionalisation in this group (64), it has limited applicability to the heart failure population and has yet to be validated in this group.

There are several different instruments used to assess frailty in individuals with heart failure. However, to date, none of these have been formally validated for use in this population. Due to the lack of validated frailty instruments in previous heart failure clinical research, caution should be exercised when interpreting the rates of frailty as they may be over or underestimated. The majority of studies included in this review have assessed frailty in community-dwelling individuals or outpatients with heart failure rather than inpatients; therefore, there is insufficient data for comparison, and there is no consensus about which time-point is most appropriate. Heart failure has been reported to be the most common cause of hospital admission in the elderly (65, 66); therefore, an opportunity exists for frailty screening to be undertaken within this large number of patients whilst they are hospitalised. This does, however, raise the question of what happens to frailty over time and whether an individual's frailty status changes when they are acutely unwell as opposed to post-discharge. The hypothesis that an individual's frailty status would be worse when they are acutely unwell, and therefore inappropriate to measure at this stage has yet to be tested in the heart failure population.

The frailty domain most commonly assessed in this group is physical function/mobility. All seven frailty instruments include a question regarding physical function, and two instruments include an objective gait speed test or handgrip strength measurement. An overview of the various domains of frailty that are assessed in each instrument is provided in Table 2.3

Individuals living with heart failure often experience disease-related deconditioning and decreased exercise tolerance which may be worse at periods of acute decompensation and hospitalisation (9); during this time, it may affect their ability to perform a physical assessment and/or handgrip strength measurement. The duration of hospitalisation should also be taken into consideration, i.e., if the hospitalisation was only one or two days, would this affect the accuracy of the frailty measurement less compared to a longer hospitalisation of greater than seven days. An individual's appetite may also be difficult to assess when

they are acutely unwell and hospitalised due to the disruption to their normal dietary habits. Furthermore, questions related to unintentional weight loss may also be difficult to assess as they are often fluid overloaded, leading to frequent changes in weight.

Table 2-3 Domains assessed in the frailty instruments identified in review.

Frailty instruments cited in articles	Physical Function/ mobility	Self-reported Physical activity level	Weight loss &/or objective weight	Self-reported exercise tolerance and/or exhaustion	Appetite	Cognition	Other (social, multi-morbidity, mood, sensory)
Frailty Phenotype	X GS HGS	X	X (SR)	X			
Deficit Accumulation Index	X		X (M)			X	X
Tilburg Frailty indicator	X HGS (SR)		X (SR)	X		X	X
CGA	X					X	X
Frailty Staging System	X					X	X
Canadian Health & Ageing Clinical Frailty Scale	X						X
SHARE-FI	X HGS	X		X	X		

Key: Self-reported (SR), Measurement (M), Gait Speed (GS), Handgrip strength (HGS)

2.8.2 Implications for practice

To the authors' knowledge, this is the first review that has focused on the frailty assessment instruments used in heart failure and the first to provide an overview of the most frequently assessed domains of frailty in this population. It is hoped that this review will help to guide future research and clinical practice on the most appropriate instrument and domains to address when assessing frailty in adults living with heart failure. This review identified that there are currently no frailty instruments that have been validated specifically for use in adults living with heart failure, resulting in uncertainty in the clinical setting regarding the optimal frailty instrument to use in this population. This review identifies that all frailty instruments assess physical function or mobility, which may not be appropriate to assess regularly in adults with heart failure. There is potential to implement routine frailty screening/assessment in adults living with heart failure in the inpatient or outpatient and or clinic setting in combination with other standardised methods of assessment. Nurses are appropriately skilled to undertake this screening as part of physical assessment, and this is a fertile area for future research**.**

2.9 Conclusion

The assessment of frailty in heart failure is an emergent research priority and is often used as an important prognostic indicator in the clinical setting. This review has highlighted the need for a validated and clinically relevant frailty assessment instrument for use in a heart failure population. Further research is also needed to gain consensus on the most appropriate time to assess for frailty in this group and to elucidate if there are significant differences in inpatient or outpatient assessment. The impact that disease-related deconditioning or progression of heart failure symptoms may have on frailty assessment also needs to be explored in future research, and the most reliable frailty domains for assessment should be chosen. Routine assessment of frailty as part of a holistic treatment plan for heart failure patients should be considered. Nurses are well placed in the acute and primary health care setting to undertake this assessment. It is imperative that frailty is being accurately and precisely assessed in this group with a validated instrument.

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Chapter 3: Methods

3.1 Preamble

Chapter 1 established the burden and significance of frailty in people living with heart failure and highlighted the importance of identifying frailty in this population. The systematic review presented in Chapter 2 discussed the suite of frailty instruments currently used in heart failure research and/or clinical practice (1) and identified that the most widely used instruments are: the Frailty phenotype (2); and Deficit Accumulation Index (3). The identified frailty assessment instruments assess several different domains, such as falls risk, depression, multimorbidity, weakness, exhaustion, poor mobility, and low physical activity. The findings emerging from the systematic review confirmed that there is an absence of global expert consensus or robust evidence regarding the optimal frailty assessment method or instrument to use in adults living with heart failure, and that little is known about the clinical implications associated with using different instruments in this population.

This chapter describes the FRAME-HF project mixed methods design, methodological underpinnings, samples, recruitment, data management processes, and the ethical and governance considerations.

3.2 Objectives

The objectives of the FRAME-HF project are to:

- establish how frailty is assessed in adults living with heart failure;
- identify which frailty domains are most frequently assessed;
- determine the association between subjective clinician estimates of frailty and formal frailty assessment in adults living with heart failure;
- evaluate the validity of frailty instruments potentially relevant for use in adults living with heart failure; and
- identify the most suitable frailty instrument(s) to use clinically to assess frailty in adults living with heart failure.

3.3 Research design

A deductive-sequential mixed methods design was considered to be the most appropriate study design to answer the FRAME-HF Project's research questions presented in Chapter 1.

This mixed methods doctoral project comprises three discrete, yet interrelated, studies with data integration occurring at the conclusion of the project, as summarised below:

- Study 1: A systematic review of frailty assessment instruments used in heart failure studies (1) (reported in Chapter 2);
- Study 2: A cross-sectional study comparing clinician estimates of frailty to formal frailty assessment in adults living with heart failure (reported in Chapter 4);
- Study 3: A two-part prospective cohort study evaluating the validity of frailty instruments potentially relevant for adults living with heart failure (reported in Chapter 5)
- Data integration: Findings from the three FRAME-HF studies (1, 4) were integrated to identify which frailty instrument/(s) is the most suitable and clinically relevant for use in adults living with heart failure (research question 4 as reported in Chapter 6).

3.3.1 Mixed method research approach

Mixed method research is a term used to describe studies that use multiple methodologies to address the research questions and objectives (5). Mixed methods is particularly useful in health research, as it allows the combination of data across multiple studies and produces more clinically meaningful and unified outcomes (6). Johnson et al. (2017) define mixed methods research as:

> *…the type of research in which a researcher or team of researchers combines elements of qualitative and quantitative research approaches (e.g., use of qualitative viewpoints, data collection, analysis, inference techniques) for the broad purposes of breadth and depth of understanding and corroboration (7) (p. 123).*

There are a plethora of mixed method designs that have evolved over time (8-10). Morse and Niehaus (2009) described eight main mixed methods design approaches (10), which Schoonenboom and Johnson (2017) (11) describe using eight 'shorthand labels and descriptions' (i.e., quantitative abbreviated to *quan*, qualitative abbreviated to *qual*, the upper-case letters denote the core data component, concurrent is indicated by the *'plus symbol'*, and sequential is indicated by the *'arrow'* symbol) as outlined below:

- QUAL + quan (inductive-simultaneous design where, the core component is qualitative, and the supplemental component is quantitative);

- QUAL→ quan (inductive-sequential design, where the core component is qualitative, and the supplemental component is quantitative);
- QUAN + qual (deductive-simultaneous design where the core component is quantitative, and the supplemental component is qualitative);
- QUAN → qual (deductive-sequential design, where the core component is quantitative, and the supplemental component is qualitative);
- QUAL + qual (inductive-simultaneous design, where both components are qualitative; this is a multimethod design rather than a mixed methods design);
- QUAL → qual (inductive-sequential design, where both components are qualitative; this is a multimethod design rather than a mixed methods design);
- QUAN + quan (deductive-simultaneous design, where both components are quantitative; this is a multimethod design rather than a mixed methods design); and
- QUAN → quan (deductive-sequential design, where both components are quantitative; this is a multimethod design rather than a mixed methods design) (p.119) (11).

As the research questions proposed by the FRAME-HF project are unable to be answered within a single study and methodology, a mixed method research design was employed. When applying Schoonenboom and Johnson's (11) mixed methods label and descriptive method from above, the FRAME-HF project is given a QUAN → qual shorthand label. Primarily, because the core data component of the project is quantitative (Cross-sectional study [Study 2] and Prospective cohort study [Study 3]); and it also utilises supplemental qualitative data approaches including: narrative synthesis (Systematic review - Study 1) and joint display table, data integration, and meta-inference techniques (Chapter 6). Data collection during the FRAME-HF project occurred in a primarily sequential manner (i.e., the studies of the project occurred in a logical sequence), therefore, a deductive-sequential (QUAN → qual) mixed method design is appropriate.

3.4 Conceptual frameworks underpinning the FRAME-HF project

As described in Chapter 1, frailty as a descriptive word has existed in English language since the 1300's (12). However, it is only since the start of the new millennia that 'frailty' has been recognised as a complex clinical syndrome (13). A syndrome is defined as: "a group of symptoms that occur together, or a condition characterised by a set of associated symptoms" (Oxford Dictionary Online) (12).

There are two main conceptual models of frailty syndrome that underpin this doctoral project: Fried's Frailty Phenotype (2); and Rockwood's multidimensional syndrome of accumulated deficits of frailty (3, 14).

The seminal conceptual literature regarding frailty syndrome was published in 2001 by Fried and colleagues and described it as a biological syndrome of age-related physical decline (2). Markers of physical frailty syndrome include decreased energy expenditure, neuroendocrine dysregulation, reduced resting metabolic rate and sarcopenia. These frailty markers are related and can be theoretically combined into a 'cycle of frailty' (2, 15). The 'cycle of frailty' provides a visual overview of the contributory factors of frailty syndrome and clinical signs and symptoms (Refer Figure 3.1).

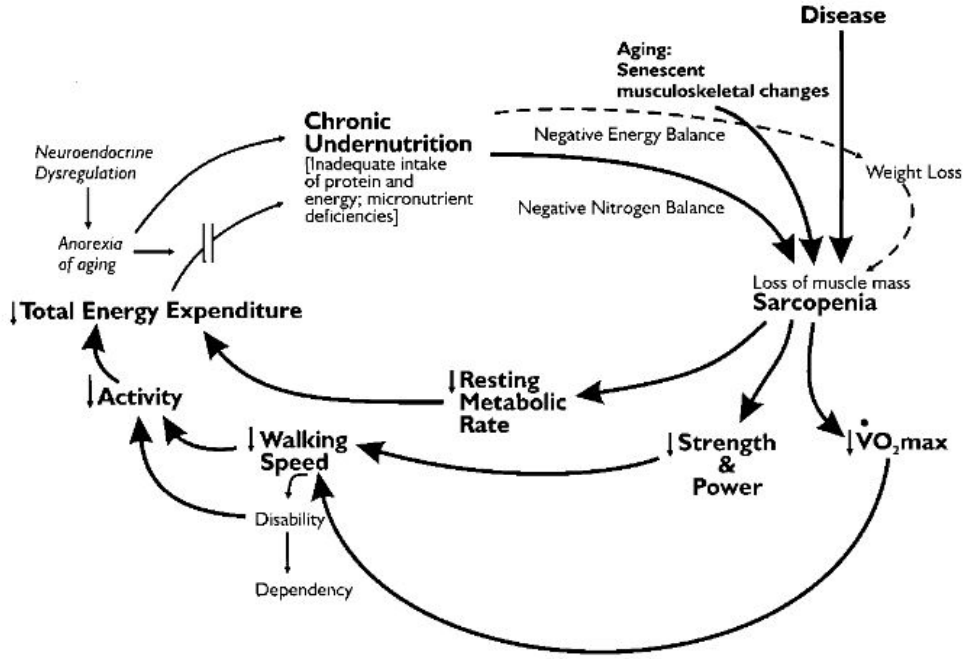

Figure 3-1 The cycle of frailty.

Image from Fried et al. 2001 (2) (p. M147), reused with permission from Oxford University Press (licence 5001130731127 Feb 02, 2021).

The second major conceptualisation of frailty was published by Rockwood and colleagues and defines it as a multidimensional syndrome of accumulated deficits (3, 14). This concept of multidimensional frailty involves assessing multiple domains of frailty (i.e., 'multi-domain'). Multidimensional frailty syndrome is hypothesized as being a consequence of accumulative deficits across multiple overlapping domains of frailty, including cognitive defects, physical deficits, lack of social support, mood disorders and undernutrition (Refer

Figure 3.2), which diminishes stress coping mechanisms and results in worsening functional decline (16).

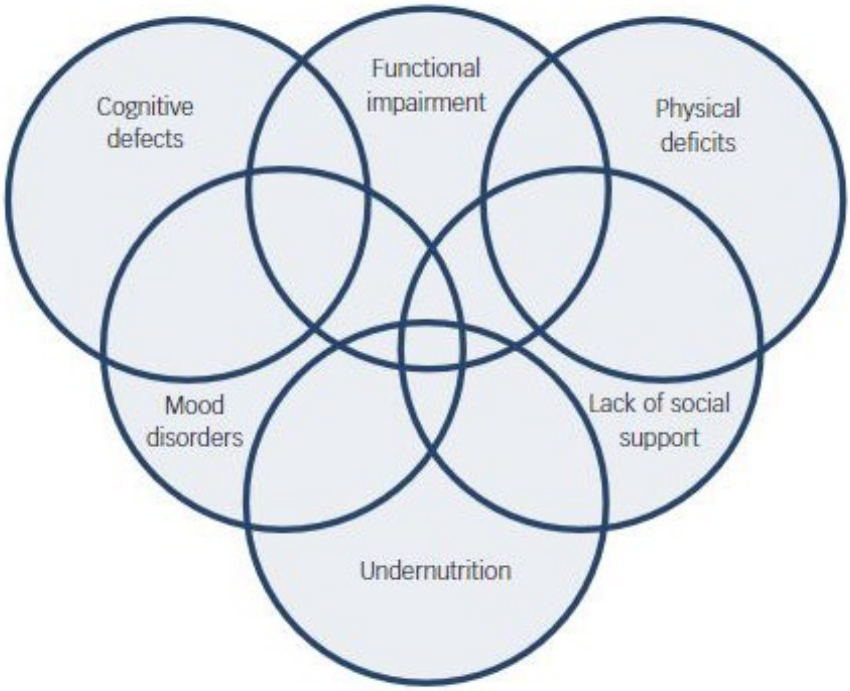

Figure 3-2 The overlapping domains of multidimensional frailty.

Image from Vitale, Spoletini, and Rosano (16) (p. 105), reused from an open-access article, which under the creative commons license, allows the reproduction of the article provided the work is adequately attributed.

As detailed in the systematic review presented in Chapter 2, there is no universally agreed-upon definition of frailty or consensus regarding the optimal means of assessing frailty in the context of heart failure (1). While physical frailty has been the focus of most frailty related heart failure research to date, there is no evidence to confirm if this is the best approach to assessing frailty in this population. Given the complexity and widespread impact of frailty on functioning, a multi-domain instrument may be more appropriate to use with people living with heart failure. Applying these two distinct conceptual models of frailty to this doctoral project was considered essential to ensuring that the frailty domains most likely to be relevant for assessment in people living with heart failure were considered.

3.5 The FRAME-HF project

The mixed methods FRAME-HF project was undertaken in 2016 and concluded in 2019. The following section details the project setting, participants, measures used and outlines the data collection processes and analysis procedures of the individual FRAME-HF studies.

3.6 Setting

The FRAME-HF project was conducted at St Vincent's Hospital Sydney, a 407-bed quaternary heart failure referral and major public teaching hospital located in Darlinghurst, an inner-city suburb of Sydney, New South Wales, Australia. This hospital specialises in heart failure management and is the only heart transplantation referral centre within New South Wales. St Vincent's Hospital Sydney was the first Australian facility to perform successful heart transplant surgery in 1984 (17). Since then, St Vincent's Hospital Sydney has maintained its reputation as a leading national and international centre for heart transplantation, performing approximately 45 heart transplants annually (17). Due to these specialised heart failure services, patient referrals are accepted from all over New South Wales and South Australia; therefore, this public hospital cares for a culturally and socio-economically diverse population.

3.7 Participants

Two cohorts of participants were included in the FRAME-HF project: a patient and a clinician sample:

- The *patient sample* included eligible people aged 18 years or older with a confirmed heart failure diagnosis (either from an echocardiogram or documented heart failure diagnosis in the medical records); and
- The *clinician sample* included cardiovascular clinicians (i.e., physicians, nurses, and allied health professionals).

All participants were recruited from the St Vincent's Hospital, Sydney inpatient cardiology ward or outpatient heart failure clinic.

3.7.1 Patient Sample

Patients were identified through convenience sampling of the inpatient cardiology ward list and outpatient heart failure clinic patient lists. Lists were screened daily by a member of the research team; any patient admitted under the heart failure specialist team or general

cardiology team for exacerbation of heart failure was reviewed against the inclusion and exclusion criteria (Table 3.1).

Patient Inclusion and exclusion criteria

Patients aged 18 years or older with a confirmed diagnosis of heart failure were eligible to take part in the FRAME-HF project. Those who were unable to provide informed consent due to dementia or another cognitive illness were excluded from the FRAME-HF studies. Patients who satisfied all the inclusion criteria and none of the exclusion criteria were invited to participate in the FRAME-HF project. All potential participants were provided with a Participant Information and Consent Form (PICF), which was explained in detail to each participant. If they were willing to participate, written consent was obtained. The complete patient inclusion and exclusion criteria is provided in Table 3.1 below.

Table 3-1 Patient inclusion and exclusion criteria.

Inclusion	**Exclusion**
• Confirmed diagnosis of heart failure (i.e., written confirmed diagnosis in medical records; and/or left ventricular ejection fraction less than 50% and/or echocardiogram findings consistent with heart failure with preserved ejection fraction) • Aged 18 years and older • English speaking • Willingness to provide informed written consent and willingness to participate to and comply with the study procedures	• Patients who had undergone heart or lung transplantation • Those with diagnosed dementia or other cognitive illness, based on confirmed and written diagnoses in the medical records, which prevented them from providing informed consent.

3.7.2 Clinician Sample

A convenience sample of cardiovascular clinicians (i.e., physicians, surgeons, registrars, interns, registered nurses, and allied health professionals), providing treatment and care to patients with heart failure in either the cardiology ward or the heart-lung outpatient clinic at St Vincent's Hospital Sydney were informed about the study during regular clinical staff meetings in the heart-lung clinic or on an ad hoc basis.

Clinician Inclusion and exclusion criteria

Nurses, physicians, allied health staff (physiotherapists, occupational therapists, and social workers) working (full-time, part-time, or permanent hospital casual pool) within the heart failure clinic and/or cardiology ward and/or providing treatment to a patient from these two clinical areas were eligible to take part. Students and temporary agency staff were excluded.

3.7.3 Measures used

Frailty instruments

As there are no validated frailty instruments available for use with adults living with heart failure, an interdisciplinary expert panel, including heart failure cardiologists, research academics, and clinical nurse specialists, considered and identified the frailty instruments most likely applicable for use within a heart failure population. This group identified six frailty instruments, which were included in the FRAME-HF project, as described below.

The Frailty Phenotype

The Frailty Phenotype was conceptualised and validated in older community-dwelling adults (n= 5317) by Fried and Colleagues (2001) using data from the Cardiovascular Health Study (2, 18). This landmark study identified five domains of physical functioning that underpinned the syndrome of frailty: shrinking (weight loss of ⩾10 pounds [5kgs] in the prior year); weakness (decreased or weakened grip strength); exhaustion (fatigue or declining endurance); (d) slowness (slower walking pace); and low activity (decline in physical activity) (2). People are considered frail if they meet three out of five of the frailty criteria listed above, pre-frail in they meet one or two of the criteria, and non-frail if they are don't meet any of the criteria. The investigators assessed the independent predictive validity of the Frailty Phenotype by examining its association with five key adverse health outcomes: incident fall, worsening mobility, activity of daily living disability, first hospitalisation, and death. After adjustment for covariates, the Frailty Phenotype remained an independent predictor of all adverse outcomes at three and seven years, with seven-year hazard ratios ranging from 1.23-1.79 ($p < 0.05$ for all accept incident fall) (2).

SHARE-FI

The SHARE –FI (The Survey of Health, Aging and Retirement in Europe – Frailty Index) was validated in community-dwelling adults (n= 31,115) from 12 European countries by Romero-Ortuno and colleagues (2010) (19). The SHARE-FI was developed as a clinically feasible

alternative to Fried's Frailty Phenotype for use in the primary care setting. The SHARE-FI uses the same five criteria as the Frailty Phenotype, except for the 'shrinkage' criteria. Instead of using self-reported weight loss to capture 'shrinkage', the SHARE-FI uses an item that measures self-reported change in appetite (19). The SHARE-FI uses an algorithm instead of the simple classification method used in the Frailty Phenotype (2), which is also available as a free online calculator that subsequently categorises people into non-frail, pre-frail, and frail. This aims to streamline the data collection process and improve the applicability of this instrument for routine clinical care.

St Vincent's Frailty instrument

The St Vincent's Frailty instrument (SVF) was adapted from Fried's Frailty Phenotype in order to improve the clinical relevance and suitability for an advanced heart failure and heart transplant candidate population (20). The SVF instrument was developed after an expert panel consultation, which included representatives from heart failure cardiology, cardiothoracic surgery, nursing staff, occupational therapy, and psychiatry. The SVF instrument involves the assessment of declining physical function across the five domains of Fried's Frailty Phenotype definition (2). People are considered frail if they meet three out of five of the frailty criteria listed above, pre-frail in they meet one or two of the criteria, and non-frail if they don't meet any of the criteria. The original Frailty Phenotype relies on entirely physical measures for each of the frailty domains assessed, including estimating calorie expenditure for the physical inactivity domain and patient-reported weight loss over the last year (2). People living with heart failure, particularly the advanced stages and those awaiting heart transplantation, often have decreased exercise tolerance and dyspnoea (21); therefore, an estimation of calorie expenditure may not be appropriate. As for the inclusion of a weight-loss domain, this too may be inappropriate in those with heart failure. Heart failure can cause fluid overload, and many patients are on a fluid restriction and are closely monitoring their weight (22); therefore, asking them about their weight loss may be an imprecise measure for this population. In the SVF instrument, 'weight loss' is replaced with a question regarding 'appetite', taken from the SHARE-FI. This question asks patients to state if they have had any appetite changes over the last month (i.e., if they are eating more or less than usual). The SVF instrument has been used in clinical practice at the study site since 2013 and has been evaluated in a cohort of adults living with heart failure who are and listed for heart transplantation (23).

The St Vincent's Frailty Plus cognitive and mood domains

The St Vincent's Frailty Plus cognitive and mood domains (SVF+) uses the same five domains from the St Vincent's frailty above plus the addition of cognitive impairment and depression domains, as measured by Montreal Cognitive Assessment (MoCA) and the Depression in medical Illness-10 (DMI-10). The total number of domains measured is seven (instead of five). People are considered frail if they meet three out of seven of the frailty criteria, pre-frail in they meet one or two of the criteria, and non-frail if they don't meet any of the criteria. The inclusion of the mood and cognitive domains transforms the Frailty Phenotype from a physical instrument to a multi-domain instrument. Increasing the number of domains from five to seven and including multiple domains rather than just physical ones aims to capture more individuals who are frail. This version of SVF+ was used in a study of adults with advanced heart failure who were listed for heart transplantation (n= 156), the results indicated that the addition of cognitive frailty measures significantly increased the ability of the frailty assessment to predict 12- month mortality compared to physical frailty assessment only (23).

The Deficit Accumulation Index

The Deficit Accumulation Index was developed by Rockwood and colleagues (3, 14) as an alternative to Fried's Frailty Phenotypic approach. The Deficit Accumulation Index takes a multidimensional view to frailty assessment and recognises that frailty causes decline in several different domains of human functioning, not just physical domains (3, 14). The Deficit Accumulation Index calculates frailty according to the number of functional, medical, or social deficits an individual has, such as cognition, activities of daily living, comorbid diseases present or abnormal laboratory results, the more deficits a person has, the higher degree of frailty. The information for the Deficit Accumulation Index is designed to be collected from routinely collected data that could be obtained from the medical records and is expressed as the ratio of health deficits present to the total number of deficits assessed (24). The number of health deficits is not fixed and can be altered to suit a certain health population or clinical setting. The Deficit Accumulation Index is strongly associated with admission to residential aged care or nursing home, and death, particularly if more than thirty deficits are assessed (3).

The Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight scale

The Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight (FRAIL) scale was developed and validated by Morley and colleagues in 2012. The FRAIL scale is a five-item scale that scores people from 0-5 (i.e., one point for each component) a score of 3-5 represents frail, 1-2 represents pre-frail, and a score of 0 robust (non-frail) (25). The FRAIL scale is a simple frailty instrument that comprises subjective questions and no objective measures. It does not require a specially trained staff and could be administered over the phone, offering another feasible solution for assessing frailty in large cohorts. The FRAIL scale was chosen because it offers another alternative to the Frailty Phenotype, but it also includes domains related to comorbidities, rather than purely physical domains, which may be more suitable and clinically relevant for use in people living with heart failure. The FRAIL scale was calculated from data collected for FRAME-HF; some of the questions were modified slightly to reduce responder burden and repetition (Appendix 2).

Table 3.2 provides an overview of the domains assessed by each frailty instrument.

Table 3-2 Domains assessed by the frailty instruments used in FRAME-HF.

	FP	SHARE-FI	SVF	SVF +	FRAIL scale	DAI
Frailty domain						
Slowness	+	+	+	+		+
Weakness	+	+	+	+		
Weight loss	+				+	+
Physical inactivity	+	+	+	+		+
Exhaustion/Fatigue	+	+	+	+	+	+
Resistance					+	+
Ambulation/Mobility					+	+
Cognitive impairment				+		+
Comorbidities					+	+
Depression				+		+
Anaemia						+
Hypoalbuminemia						+
Poor appetite		+	+	+		+
Functional status/self-care						+
Polypharmacy						+

Key: FP, Frailty Phenotype; SHARE-FI, Survey of Health, Ageing and Retirement in Europe Frailty Instrument; SVF, St Vincent's Frailty Instrument; SVF +, St Vincent's Frailty Instrument plus cognitive and mood domains; FRAIL scale, Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight scale; and DAI, Deficit Accumulation Index.

Other physical and psychosocial measures

Additional measures were used in this project. They assess comorbidities pertinent to the management of both heart failure and frailty provide additional information required for the multi-domain frailty assessment and the participant clinical profiling. These additional measures are described below.

The Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) (Version 7.1) is a validated tool to assess mild cognitive impairment (26). The MoCA assesses cognitive functioning in the areas of visuospatial/executive thinking, naming, memory, attention, language, abstraction, delayed recall, and orientation; a score of less than 26 is indicative of mild cognitive impairment (26). The MoCA was chosen as it has displayed adequate sensitivity for detecting mild cognitive impairment in people living with heart failure (27). For the FRAME-HF project, a MoCA was used only to collect data, not to diagnose cognitive illness or impairment. If a patient was found to have an abnormal MoCA score after informed consent had already been obtained, they were still included in the project.

The Depression in Medical Illness-10 questionnaire

The Depression in Medical Illness (DMI-10) questionnaire was used to assess depression. The DMI-10 focuses on ten areas of mood and has a Likert scale of four responses: not true, slightly true, moderately true, and very true. A score of at least nine is indicative of probable or definite depression (28). Depression is common in both heart failure and frailty (29), and depression screening using the DMI-10 has been shown to increase the predictive ability of a frailty assessment (23).

EuroQoL5D-5L

The EuroQoL 5D-5L (EQ5D-5L) is a validated generic self-reported quality of life instrument, comprising five questions with five possible response levels (30). It also includes a visual analogue scale that asks participants to rate their 'health state today' from 0 – 100. The EQ5D-5L was selected as it is brief and less burdensome to complete. It includes self-reported items related to physical function, self-care, and mood, which are all domains regularly assessed in many frailty instruments (31).

Australian-modified Karnofsky Performance Scale

The Australian-modified Karnofsky Performance Scale (AKPS) is a validated scale that was modified for the Australian population in those receiving palliative care treatment (32). The AKPS is an 11-point rating scale from 0 – 100 that assesses an individual's performance status across three dimensions: activity, work, and self-care. The scale is clinician-rated and scores individuals from 0 (dead) to 100 (normal, no complaints, no evidence of disease). The AKPS scale has also been shown to correlate with New York Heart Association (NYHA) class (33). For the FRAME-HF project, a score of less than 70 (Cares for self, unable to carry on normal activity or active work) was considered to be abnormal.

Charlson Comorbidity Index

The Charlson Comorbidity Index was developed and validated by Charlson and colleagues in 1987 (34). The index is a valid, prospectively applicable method of classifying comorbid conditions and can predict the risk of death from comorbid disease for use in longitudinal studies. The adapted new version of the index (35) was used in FRAME-HF.

The FRAME-HF project case report forms are provided in Appendix 3.

3.7.4 The FRAME-HF studies

As outlined in Chapter 1, The FRAME-HF project comprises three discrete but interrelated studies: a systematic review (Study 1), a cross-sectional study (Study 2), and a prospective cohort study (Study 3). Figure 3.4 provides a visual overview of the project flow and how each of the studies are connected.

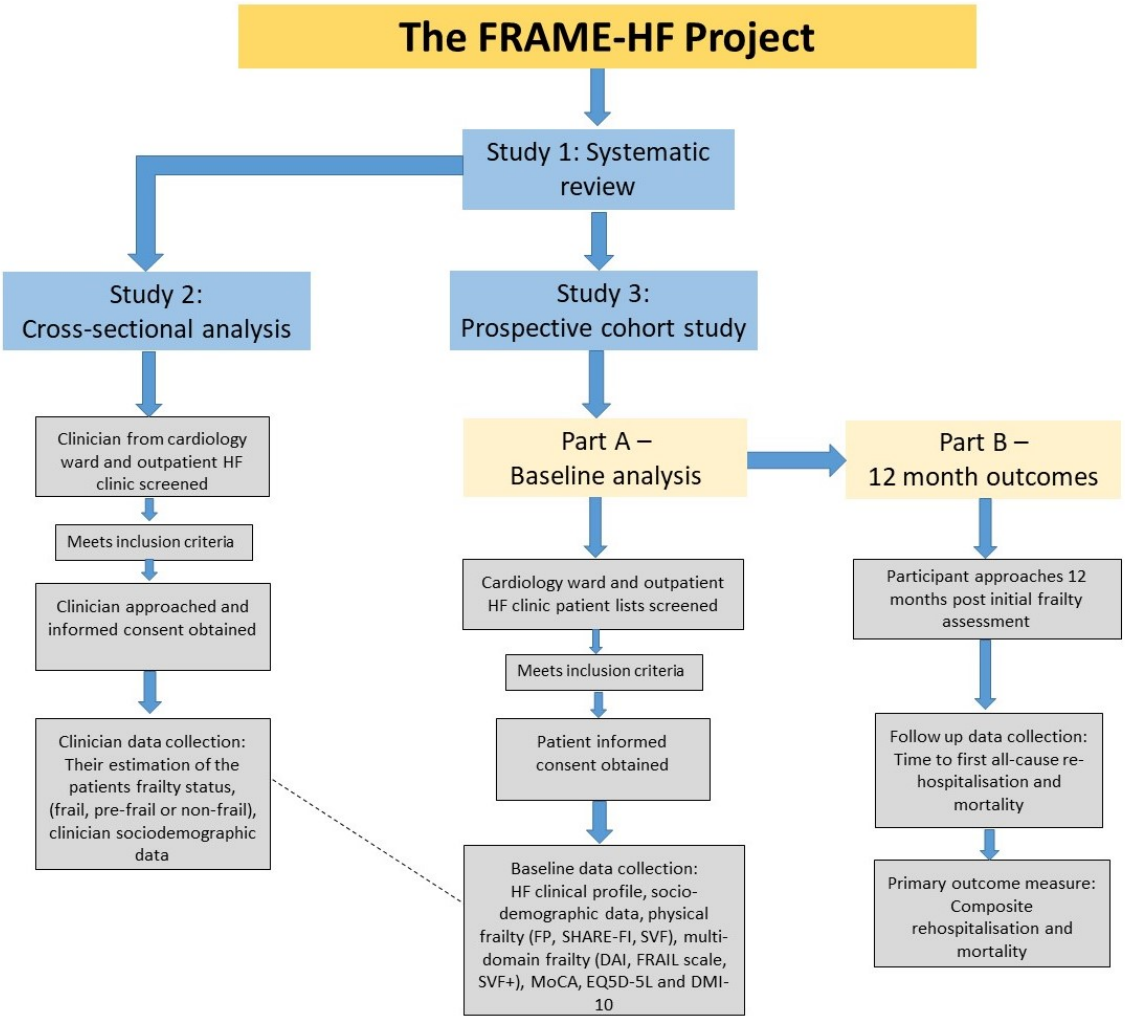

Table 3-3 The FRAME-HF project flow diagram.

Note: Study 2 uses the clinician sample and patient sample data, Study 3 uses only the patient sample; the broken line between Study 2 and 3 indicates that the clinician frailty estimate data is paired to the patient frailty data.

Timing of the FRAME-HF studies: The studies of the project occurred in a primarily sequential manner, with staggered data collection. However, parts of Study 2 and Study 3 were undertaken concurrently. Study 2 was a cross-sectional study which aimed to include approximately the first 80 patient participants recruited as part of Study 3 and also

separately recruited the clinician participants. Both Study 3 and Study 2 began recruitment in August 2016. Study 2 reached the intended number of participants in July 2017, however, recruitment and data collection for Study 3 continued until February 2018. Follow up data for Study 3 were collected at 12 months post initial frailty assessment, which was completed in February 2019. Trained heart failure research nurses Julee McDonagh (JM) and Roslyn Prichard (RP) recruited the participants and collected the FRAME-HF project data. The methodology, data collection and analysis procedures for each of the FRAME-HF studies are described in this section.

Study 1: Systematic review

The Systematic review methodology has been reported in Chapter 2.

Study 2: Cross-sectional study

Aim: To compare subjective clinician estimates of frailty to a formal frailty assessment in adults living with heart failure.

Design: Cross-sectional study comparing clinician estimates of frailty to formal frailty assessment using the St Vincent's Frailty instrument in adults living with heart failure.

Participants: Patient sample and clinician sample as described in Section 3.7.

Data collection: Patient sample data were collected as part of the prospective cohort study (Study 3, as described below). Once a patient participant had been recruited from the heart failure clinic or the cardiology ward, and baseline data collection was complete, clinicians caring for a patient recruited into the Study 3 were screened and approached by RP and invited to take part, and if willing, informed consent was obtained. Once a clinician completed the informed consent process, they were given a clinician frailty estimate questionnaire. The questionnaire captured a range of variables, including their estimation of the patient's frailty status (frail, pre-frail, or non-frail), their socio-demographic details (age, sex, how long they'd known the patient for, professional group [nurse, allied health professional or physician] and years of experience in current profession). Once a clinician was recruited, if willing, they were able to complete the frailty estimate questionnaire on multiple patients (capped at 10 patients per clinician).

Analyses: All statistical analyses were completed using SPSS version 26 (IBM Corp, NY Amarok).Reporting and analysis of data were completed in-line with recommendations from

the Strengthening and the Reporting of Observation Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies (36) and were guided by an experinced biostatistician. Patient and clinician characteristics were analysed using descriptive statistics. Categorical data were expressed as frequency, percentage, and continuous data presented as mean and standard deviation. Frailty was analysed according to formal frailty assessment (using the St Vincent's Frailty Instrument) and clinician-estimated frailty, with frailty classifications of each group expressed as frail, pre-frail, or non-frail for both groups. Formal and clinician-estimated frailty classifications, stratified by clinician professional group (nurses, allied health, and physician) and patient characteristics (sex, inpatient/outpatient, and NYHA Class), were also analysed.

The correlation between clinician-estimated frailty and formal frailty were assessed using Spearman's correlation coefficient: with a coefficient > 0.40 considered fair correlation, >0.60 considered moderate correlation and, >0.80 considered very strong correlation (37).

The inter-rater agreement between the clinician-estimated frailty and formal frailty were assessed using a linear weighted Kappa statistic: with > 0.20 indicating fair agreement, >0.40 indicating moderate agreement and, >0.60 indicating good agreement (38).

Study 3: Prospective cohort study

Aim: To evaluate the validity of frailty instruments potentially relevant for use in adults living with heart failure.

Design: Prospective cohort study with a 12-month follow period. A prospective cohort study is a form of an observational cohort study that involves collecting data about an individual or group over a long period of time and then following the participants to measure specific outcomes (39). A prospective cohort design was chosen as it allowed participants to have their frailty assessed and then followed up for 12 months to evaluate the association between being frail and the main study outcome of rehospitalisation and/or mortality.

This prospective cohort study consisted of two parts: Part A focused on evaluating the convergent and discriminant validity of three Physical frailty instruments (the Frailty Phenotype, the SHARE-FI, and the SVF); and Part B focused on the predictive performance of six frailty instruments (the three physical frailty instruments above and the SVF+, the Deficit Accumulation Index, and the FRAIL scale).

Participants: This study involved participants from the patient sample described above (Refer Section 3.7.1)

Reporting and analysis of data were completed in-line with recommendations from the Strengthening and the Reporting of Observation Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies (36) and were guided by an experienced biostatistican.

Study 3 – Part A

Data collection: Part A was the baseline data collection phase. A standardised case report form was developed for the study, which was informed by the literature and in partnership with an interdisciplinary expert panel including heart failure cardiologists, research academics, and clinical nurse specialists. After informed consent was received, patient baseline data collection took place on the cardiology ward or in the heart failure clinic waiting room. It included: socio-demographical information, patient medical history, pathology results, blood pressure, cardiac rhythm, current medications, depression screening, quality of life, functional status, and frailty assessment (according to six different instruments: the Frailty Phenotype (2); the SHARE-FI (19); the SVF (20); SVF+ and depression; the Deficit Accumulation Index (3); and the FRAIL scale (25)).

Analyses: All statistical analyses were computed using IBM SPSS Statistics version 25 (Armonk, NY: IBM Corp). Demographic and clinical characteristics were summarised using descriptive statistics; continuous data were summarised using means ± standard deviation for normally distributed data or median (inter-quartile range) for non-parametric data. Categorical variables were summarised using frequencies and percentages.

Convergent validity was assessed using Pearson's Correlation coefficient to report the correlation between the three physical instruments and five heart failure-related sub-constructs. The sub-constructs chosen were heart failure - related functional capacity (NYHA), Quality of life (EQ-5D-5L), functional status (AKPS), cognitive ability (MoCA), and depression (DMI-10). It was hypothesised that these sub-constructs are associated with both frailty and heart failure and that patients assessed as frail would also score poorly in the sub-construct assessments.

Discriminant validity was assessed using group comparison analysis and the chi-square test. The ability of each physical instrument to discriminate between normal and abnormal scores of the sub-constructs according to frailty classification (frail, pre-frail and non-frail) was analysed. For the group comparisons, the one-sample Kolmogorov-Smirnov test indicated that none of the continuous variables were normally distributed; these variables were dichotomised at the median (40). The threshold for statistical significance was a *p*-value of <0.05.

Study 3 – Part B

Data collection: Part B was the outcome data phase. Outcome data were collected at 12 months post initial frailty assessment and included the incidence of the first all-cause rehospitalisation and/or mortality for each participant. An excel table with the study identification number of each patient was used, which calculated when a patient was approaching their 12-month follow-up. When each patient had reached 12 months, the research nurse (JM) checked the study site hospital intranet and collected the data about the first rehospitalisation: date, duration, location, and cause of admission (i.e., heart failure-related or not). Mortality data (i.e., date of death) was also collected from the study site hospital intranet. If there was no information available for a patient after baseline, JM telephoned the patients, and if willing, the patients themselves kindly provided this information, or the next of kin if the patient had passed away or was unavailable.

Analyses: All statistical analyses were performed using IBM SPSS statistics version 26 (IBM Corp, NY Amarok). The performance of the six frailty instruments at predicting composite all-cause first rehospitalisation and mortality were compared. All frailty instruments were analysed using a dichotomous variable: frail or non-frail. Baseline socio-demographic and clinical characteristics were summarised using descriptive statistics stratified into frail and non-frail according to the six frailty instruments. Continuous data were summarised using means ± standard deviation and compared using the analysis of variance test (ANOVA). Categorical variables were summarised using frequencies and percentages and compared using the chi-squared test. A p-value of < 0.05 was the threshold for statistical significance.

Multiple logistic regression was used to create six frailty instrument models which evaluated the association between each frailty instrument and all-cause rehospitalisation and mortality at 12-months, adjusting for potential confounding factors. The dependant variable

was a composite of 12-month rehospitalisation and mortality event data (no event = 0, event = 1). Frailty, according to the six different instruments, was used as the independent variable, and each model was adjusted for: age, sex, albumin and estimated glomerular filtration rate (eGFR). These potential confounding variables were selected for inclusion in the final models based on subject matter knowledge, previous publications (20, 41) and statisical judgement. The odds ratio for composite rehospitalisation and mortality was indicated by the Exp(B) statistic in the model, with confidence intervals of 95 per cent requested. Sensitivity and specificity were analysed using the cut-point of >0.5. The predictive performance of each frailty instrument model was also compared by plotting receiver operating characteristic (ROC) curves and calculating C-statistic values (area under the curve). The C-statistic indicates how good a model is at correctly classifying outcomes, with a value of >0.70 considered acceptable discrimination.

3.7.5 Data integration

Integration is the process of combining data from multiple research methods together to generate knowledge or insights unavailable to single method studies (42). As this doctoral project uses a combination of both quantitative and qualitative data approaches, a procedure for the integration of findings is important. Fetters et al. (2013) describe approaches of achieving integration in mixed methods research across three integration levels, i.e., the study design level, the methods level, and the interpretation and reporting level (43). The principle and practices for integration proposed by Fetters et al. were used to guide the integration approach for this doctoral project (43).

The point of integration for this doctoral project was at the interpretation and reporting level. Integration at the interpretation and reporting level can occur in three ways, i.e., through narrative, data transformation, and joint displays (43). The FRAME-HF project data was first integrated through narrative. The data from the individual studies were presented in a single report addressing the project's research questions outlined in Chapter 1, and secondly using joint display (presented in Chapter 6). A joint display table provides a visual overview of the combined project findings and allows meta-inferences to be drawn. Meta-inferences are the overall conclusions, explanations, or understanding developed through combining the inferences obtained from a mixed method study (9, 44, 45). The use of a joint display table in this final narrative report generated meta-inferences which were used to

answer the final research question of the project: “Which frailty instrument/(s) is the most suitable and clinically relevant for use in adults living with heart failure?” The integration of the FRAME-HF data also generated a series of clinical recommendations for practice and future research which will be presented at the conclusion of Chapter 6.

3.8 Data storage

Data storage was managed with guidance from the IMPACCT Standard Operating procedure 5.23.2 Data Collection Worksheet Completion and 5.5.1 Electronic Data Handling (46, 47). The Data was recorded onto the case report form using tick boxes and was only entered in the allocated space; any additional free-text data was initialled and dated to avoid any post data collection entry or errors. Once study data were collected on the paper case report form it was then entered into REDCap electronic data capture tools hosted at The University of Technology Sydney (48, 49). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to standard statistical packages; and 4) procedures for data integration and interoperability with external sources, an online data storage system. A benefit of REDCap is that it is straightforward to use and is secure. For this study, only three of the study personnel had access to it. The paper data files were stored in a locked filing cabinet within a locked room that only minimal people have access to. The data will be kept on hospital ground for a minimum of five years and then destroyed after this time. All data files were kept de-identified with only the initials and study identification number of the patient recorded on the file. The screening log with full-patient name and contact information was kept on a shared drive as part of the clinical hospital computer network of the study site which only the two research nurses (JM and RP) had access to.

3.9 Ethical and governance considerations

The FRAME-HF project conforms to the standards outlined in the Declaration of Helsinki (50). FRAME-HF was classified as ‘low and negligible risk’ and after submission of the ‘Low and Negligible Risk Site-Specific Assessment’ and the ‘National Ethics Application Form’ was approved by the St Vincent’s Hospital Human research ethics committee (HREC 16/204) and ratified by the University of Technology Sydney Human Research Ethics committees (UTS

HREC REF NO. ETH16-0593) (Refer Appendix 4). The PICF provided detailed information to the participant about potential risks and contact details for the study coordinator in the case of any study-related problems or if the participant wished to withdraw from the study.

The FRAME-HF project was designed with careful consideration for the following ethical codes:

3.9.1 Research merit, integrity, and honesty

FRAME-HF was designed to fill an identifiable gap in the knowledge. Following a systematic review of the available evidence to justify the need for this study, the ethics application and PICF were also deemed to be appropriate and feasible. The project did not expose participants to unnecessary harm or risk and was conducted by a team with the required expertise and current good clinical practice certification (GCP). The project investigators were committed to undertaking the FRAME-HF project honestly and with integrity throughout the whole process, which included disseminating all the results, both positive and negative, and working closely within the study site and university ethical guidelines and processes to ensure no research misconduct occurred.

3.9.2 Justice and beneficence

The ethical principle of justice requires fairness in dealing with others, which the FRAME-HF investors held in extremely high regard. All participants were given adequate information in the PICF regarding the study procedures, the participant's involvement, details of the researcher's role and responsibilities before making an informed agreement to participate.

The ethical principle of beneficence denotes that the likely benefit of research must outweigh any potential harms, which was carefully considered when designing FRAME-HF. From an ethical perspective, the observational nature of this project and lack of control or intervention is deemed to be 'low risk'. However, it was acknowledged that certain aspects of the study, such as completing the cognitive, depression, and quality of life screening, may have the potential to cause anxiety or trigger negative mental health concerns. In this case, participants were offered the appropriate counselling from qualified health practitioners within the study site health service.

3.9.3 Respect for cultural diversity

This project was undertaken in a health setting with participants from diverse cultural backgrounds, including First Nation's people. Respect for cultural diversity and cultural safety during this project was of particular importance. For First Nations peoples, particular care was taken to ensure that cultural identity was respected at all times and that all study measures were delivered in a culturally safe environment. Unfortunately, a lack of funding prohibited the use of an interpreter or translator service to translate the PICF and case report forms into other languages; therefore, people who could not read or speak English were unable to take part in this project.

3.9.4 Autonomy, individual responsibility, and informed consent

The informed consent process was undertaken with respect to the patient and clinician's autonomy and their right to make decisions about what happens to them based on their personal beliefs and values. Patients were invited to participate and provided with information related to the project by the study coordinator. They were allowed to read the information and ask any questions before consent was sought. The participant was enrolled in the project after the informed consent process had been completed, and the participant had met all inclusion criteria and none of the exclusion criteria. The participant was given a project enrolment identification number which was documented in the participant's medical record and on all project documents.

3.9.5 Privacy and confidentiality

Respect for the participants' privacy (patient and clinician) was carefully considered. During the informed consent process, participants were informed that all information held by the project team would be de-identified using a project ID number. They were also informed that project results would likely be published, but no individual patient or clinician personal details would be exposed.

3.10 Conclusion

This chapter has described the methodological processes, data management and analysis procedures, and ethical and governance considerations of the FRAME-HF project. The following chapter will present the results of Study 2, which will investigate the reliability of subjective clinician estimates of frailty compared to conducting a formal frailty assessment.

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Chapter 4: Clinician estimates of frailty compared to formal frailty assessment in adults with heart failure: a cross-sectional study

4.1 Preamble

Chapter 1 defined frailty in the context of heart failure, highlighting the two main conceptualisations of frailty. Chapter 2 described how frailty is assessed in adults living with heart failure, identifying seven different instruments used across 20 heart failure studies. Yet, there is currently no accepted definition of frailty or recommendations regarding the optimal means of assessing frailty in a heart failure population. Consequently, frailty is often identified in the clinical setting using subjective estimates rather than a formal instrument. The accuracy of these subjective estimates in determining the frailty status of those with heart failure is largely unknown. This chapter will present a comparison of clinician-estimated frailty and formal frailty assessment in adults living with heart failure.

4.2 Publication reference for Study 2

This chapter contains a slightly modified version of a submitted manuscript currently under review in a Q1 Journal.

> **McDonagh J**, Prichard R, Ferguson C, Phillips JL, Davidson PM, Macdonald PS, Newton PJ. Clinician estimates of frailty compared to formal frailty assessment in adults with heart failure: a cross-sectional analysis. 2021; Heart, Lung and Circulation (Under Review).

4.3 Introduction

Frailty is common in adults living with heart failure, with prevalence ranging from 15-79% and is independently associated with mortality and rehospitalisation (1-3). Frailty was conceptualised by Fried and colleagues in 2001 as a biological syndrome that causes age-related physical decline (4). Since then, numerous instruments have been developed to assess frailty (5), all of which display different strengths and weaknesses in the assessment of patients with heart failure (6). Frailty instruments are generally categorised into two broad groups: those that focus on the biological physical phenotype of frailty (4); or use a multidimensional deficit accumulation method (7, 8). A recent systematic review identified the Frailty Phenotype (4) as the instrument most commonly used in patients with heart

failure (3). The Frailty Phenotype classifies someone as frail if they display three or more of the following criteria: weak hand grip strength, slow walking speed, and self-reported exhaustion, physical inactivity, or unintentional weight loss (4).

A formal frailty assessment, conducted using a validated instrument, as opposed to subjective clinical judgement, is recommended in international guidelines (6, 9-11). However, ambiguity regarding the universal definition of frailty and the lack of a validated instrument for use in patients with heart failure (3), as well as systems-related factors (e.g., lack of education, time, and equipment) limits the routine assessment of frailty in clinical practice (6, 12). Instead of conducting a formal frailty assessment, clinicians often rely on subjective estimates of frailty, such as the *'end-of-the-bed'* or *'eyeball'* test to identify frailty and determine suitability for advanced therapies and/or surgical intervention (6, 12-18). The *'eyeball'* test's accuracy was compared to a statistical risk estimate model in a large population of consecutive patients undergoing cardiac surgery (n= 5099) (16). The statistical risk estimates model was a better predictor of post-surgical mortality than the physician's subjective *'eyeball'* test. (16). The association between subjective estimates of frailty and formal frailty assessment in patients with heart failure is largely unknown. Therefore, this study sought to compare a clinician estimate of frailty to formal frailty assessment in adults living with heart failure to determine this form of assessment's efficacy.

Aim:

To examine the association between clinician-estimated frailty and formal frailty assessment in adults living with heart failure.

4.4 Methods

A detailed overview of the methods was provided in Chapter 3. A brief description of the study measures used, and the analyses undertaken is provided here.

All participants had their frailty formally assessed by the clinical trial nurses, using a modified version of the Frailty Phenotype (4) which classifies patients as either: frail, pre-frail, or non-frail, based on the same five phenotypic frailty criteria as the original Frailty Phenotype but replaces self-reported 'unintentional weight loss' with 'decreased appetite' and uses self-reported 'decrease in physical activity' instead of decreased kilocalorie expenditure (19, 21).

Once the patient's formal frailty assessment and baseline data collection were complete, clinicians were invited to take part in the study, and if willing, informed consent was obtained. The clinicians, blinded to the formal frailty assessment outcomes, completed their routine clinical assessment of each FRAME-HF patient. After completing their routine clinical assessment, clinicians were asked to rate the participant's frailty status: frail, pre-frail, or non-frail. The clinicians could provide estimates on up to a maximum of ten patients over the study period. Multiple clinicians could provide an estimate on the same patient; however, in those instances, the clinicians were blinded to the previous estimates.

4.4.1 Statistical analysis

Frailty was analysed according to formal frailty assessment using a modified version of the Frailty Phenotype ('formal frailty') and subjective estimation of frailty ('clinician-estimated frailty'), with frailty classifications of each group expressed as frail, pre-frail, or non-frail.

It was hypothesized that patients who were admitted to hospital, and those classified as NYHA class III and IV may be more easily identifiable as frail, therefore, formal, and clinician-estimated frailty classifications, stratified by clinician professional group (nurses, allied health, and physician) and patient characteristics (inpatient/outpatient, New York Heart Association Class and sex), were analysed. Sex was analysed to determine the effect that patient sex (male/female) had on the ability of clinicians to estimate frailty.

The correlation between clinician-estimated frailty and formal frailty were assessed using Spearman's correlation coefficient: with a coefficient > 0.40 considered fair correlation, >0.60 considered moderate correlation and, >0.80 considered very strong correlation (25).

The inter-rater agreement between the clinician-estimated frailty and formal frailty were assessed using a linear weighted Kappa statistic: with > 0.20 indicating fair agreement, >0.40 indicating moderate agreement and, >0.60 indicating good agreement (26).

4.5 Results

4.5.1 Participants

A total of 75 patients and 39 clinicians were recruited, producing 194 paired frailty assessments. The mean age of the patients was 54 years (± 13), more than two-thirds were male (n= 50, 67%) and NYHA Class II and III (n= 51, 68%) (Refer Table 4-1). The majority of

the clinicians were aged between 26- 45 years (n= 29, 75%) and female (n=28, 71%). Registered nurses comprised the largest group of clinicians (n= 23, 59%) (Refer Table 4-2).

Table 4-1 Patient characteristics.

Patient	**n= 75**
Age, mean (SD)	53 (± 13)
Sex (male), n (%)	50 (67)
NYHA I, n (%)	10 (13)
NYHA II, n (%)	26 (35)
NYHA III, n (%)	25 (33)
NYHA IV, n (%)	12 (16)
Patient status (inpatient), n (%)	25 (33)
Frail or pre-frail	58 (77)
Left ventricular ejection fraction	29 (15)
Impaired cognition (MoCA <26), n (%)	26 (35)
Depression (DMI-10 ≥ 9), n (%)	22 (29)
Self-reported health state rating VAS, n (%)	54 (21)

Key: MoCA (Montreal Cognitive Assessment), DMI-10 (Depression in Medical Illness questionnaire, VAS (Visual analogue scale).

Table 4-2 Clinician characteristics.

Clinicians	**n = 39**
Age group	
25 or younger, n (%)	3 (8)
26-35, n (%)	21 (54)
36-45, n (%)	8 (21
46-55, n (%)	4 (10)
Over 55, n (%)	3 (8)
Sex (female) n (%)	28 (71)
Professional group	
Allied Health, n (%)	5 (13)
Nursing, n (%)	23 (59)
Medical, n (%)	11 (28)
Years of experience	
<5 yrs	7 (18)
6-10 yrs	18 (46)
11-20 yrs	10 (26)
21-30 yrs	2 (5)
>30 yrs	2 (5)

4.5.2 Frailty estimates

Clinicians overestimated the 'non-frail' group by more than twofold (44% clinician-estimated frailty vs 21% formal frailty) but underestimated those who were 'pre-frail' and 'frail' (Table 4-3). When stratified by professional group (allied health, nurse, or physician), frailty was under-estimated by all three groups (Refer Table 4-3). Clinicians' underestimated frailty in both inpatients and outpatients (Refer Table 4-4). Frailty was misclassified in both males and females, particularly, in the 'pre-frail' category, with 38% (n= 21) estimated as pre-frail by clinicians compared to 70% (n= 39) formally assessed as 'pre-frail'. When stratified by NYHA class III-IV, 25% (n=21) were estimated as 'frail', compared to 45% (n= 46) formally assessed as 'frail'. NYHA class I-II was also associated with misclassification, with 59% (n= 54) estimated as 'non-frail' compared to 27% (n= 25) formally assessed as 'non-frail' (Refer Table 4-4).

Table 4-3 Clinician-estimated frailty and formal frailty classification: pooled clinician estimates and stratified by clinician professional group.

	Non-frail		**Pre-frail**		**Frail**	
	Formal n (%)	Clinician n (%)	Formal n (%)	Clinician n (%)	Formal n (%)	Clinician n (%)
Pooled clinician n= 194	42 (21)	88 (44)	102 (51)	77 (39)	50 (25)	29 (15)
Nurse n= 109	24 (22)	48 (44)	59 (52)	44 (40)	26 (24)	17 (16)
Physician n= 58	12 (21)	24 (41)	30 (52)	26 (45)	16 (28)	8 (14)
Allied-health n= 26	6 (23)	15 (58)	12 (46)	7 (27)	8 (31)	4 (15)

Table 4-4 Clinician-estimated frailty and formal frailty classification stratified by patient gender, patient status and NHYA class.

	Non-frail		**Pre-frail**		**Frail**	
	Formal n (%)	Clinician n (%)	Formal n (%)	Clinician n (%)	Formal n (%)	Clinician n (%)
Male n= 138	40 (29)	61 (44)	63 (46)	56 (41)	35 (25)	21 (15)
Female n= 56	2 (4)	27 (48)	39 (70)	21 (38)	15 (27)	8 (14)
Inpatient n= 62	7 (11)	16 (26)	21 (34)	29 (47)	34 (55)	17 (27)
Outpatient n=132	35 (27)	72 (55)	81 (61)	48 (36)	16 (12)	12 (9)
NYHA Class I – II n= 92	25 (27)	54 (59)	63 (69)	34 (37)	4 (4)	4 (4)
NYHA Class III – IV n= 102	17 (17)	34 (33)	39 (38)	43 (42	46 (45)	25 (25)

Correlation

Correlation between clinician-estimated frailty and formal frailty was fair (r_s = 0.52, p= <0.00). Nurse-estimated frailty was the least correlated to the formal frailty (r_s = 0.48, p=<0.00), with the strongest correlation found between the allied health-estimated frailty and formal frailty (r_s =0.71, p= <0.00) (Refer Table 4-5).

Inter-rater agreement

Agreement between clinician-estimated frailty and formal frailty was fair (0.33, CI: 0.23 - 0.43, p= <0.00), however, when stratified into professional group, allied health-estimated frailty showed moderate agreement (0.45, CI: 0.22 – 0.68, p= <0.00) (Refer Table 4-5).

Table 4-5 Association between clinician-estimated frailty and formal frailty assessment.

	Correlation coefficient	Weighted Kappa
Frailty estimates (all clinicians) n= 194	r_s = 0.52 p= <0.00	0.33 (95% CI: 0.23 -0.43) p= <0.00
Nurse- estimated frailty n= 109	r_s = 0.48 p= <0.00	0.29 (95% CI: 0.15 – 0.43) P= <0.00
Physician-estimated frailty n= 58	r_s = 0.54 p= <0.00	0.34 (95% CI: 0.16 – 0.52) P= <0.00
Allied health-estimated frailty n= 26	r_s = 0.71 p= <0.00	0.45 (95% CI: 0.22 – 0.68) P= <0.00

Note: Correlation is between estimated and formal frailty and was assessed using Spearman's correlation coefficient. Weighted kappa is agreement between estimated and formal frailty. Key- CI: Confidence Interval.

4.6 Discussion

This comparison of subjective clinician-estimated frailty to formal frailty assessment using a modified version of the Frailty Phenotype revealed that clinicians' generally underestimated frailty, frailty misclassification was common, and clinician estimates of frailty did not show strong correlation or agreement to the formal frailty assessment. Of the three professional groups, allied health clinician frailty estimates showed the strongest agreement and correlation to the formal frailty assessment over the pooled clinician-estimated frailty and the other two professional groups, though this was only moderate. In this study, the allied health clinicians included occupational therapists and physiotherapists who may have had experience undertaking frailty assessments as part of their clinical role. At the study site, allied health staff conduct regular frailty assessments, using the modified version of the Frailty Phenotype (4, 21, 22), as part of heart and lung transplant workup, as well as other routine physical and functional health assessments on patients, making them potentially well placed to estimate patient frailty status. In contrast, cardiovascular nurses and physicians are not generally required to undertake regular formal frailty assessments at the study site, which may have limited their capacity to competently estimate patient frailty status based on their routine clinical assessment.

Frailty assessment findings help inform the study site's multi-disciplinary heart and lung transplantation team discussions regarding potential interventions and treatment plans.

Therefore, the clinicians in this study are more likely than others to have a general understanding of the concepts and clinical implications of frailty; however, this exposure did not increase their ability to subjectively assess their patient's frailty.

Similar findings have been found in other studies (15, 27, 28). A prospective study of hospitalised cardiology patients (n= 47) demonstrated that agreement between estimated and formal frailty was poor, leading the authors to conclude that clinician estimates of frailty are unreliable (15). Similarly, another study of adults undergoing haemodialysis (n= 146) found that per cent agreement between clinician- perceived frailty and formal frailty (using the Frailty Phenotype) criteria was poor. These authors concluded that perceived frailty is an inadequate proxy for formal frailty (27). A cross-sectional analysis of community-dwelling adults aged 60 years or older (n= 78) also demonstrated a general practitioner-estimate of frailty was poorly correlated to overall frailty using a validated instrument (28). Despite these findings, subjective estimation of frailty continues to be applied in clinical practice (18, 29, 30).

In FRAME-HF Study 2, there was a disparity between the clinician-estimated and formal frailty assessments. Interestingly, when stratified by NYHA class, the classification of frailty between estimated and formal frailty remained divergent, suggesting that NYHA class did not affect how the clinicians estimated patient frailty. Patients classified as NYHA class IV are considered to be 'unable to carry out any physical activity without discomfort', and they 'experience symptoms at rest' (31) and have previously demonstrated significantly higher frailty prevalence compared to those classified as NHYA class III ($p = < 0.001$) (21). Therefore, it was assumed that patients with NYHA class IV symptoms would be more easily identifiable as frail, but this was not the case. When stratified by patient status (inpatient or outpatient), the frailty classifications between estimated and formal frailty were similarly divergent. Inpatient assessments were more associated with frailty misclassification in the inpatient 'frail' group. Conversely, the outpatient 'pre-frail' group were misclassified by almost half (36% clinician-estimated vs 61% formal).

These results provide an example of how frailty is perceived in the clinical setting. Frailty misclassification was high and clinicians' generally underestimated frailty. It is easy to wrongly assume that frail individuals are all stooped nonagenarians or that younger heart failure patients are non- frail. Yet, despite the patient cohort being middle aged, three-

quarters were classified as being frail or pre-frail. With the lower age of the cohort, it is possible that many of the patients did not necessarily 'look frail'. These results, similar to others (27, 28), demonstrate that frailty is fundamentally difficult to identify with a subjective clinician estimate. As mentioned, the patients with NYHA class IV symptoms were poorly identified as frail by clinicians in this study. In another study of patients with advanced heart failure referred for heart transplantation (n= 120), frailty was also identified in participants with body mass index category 'overweight' and 'obese' (21), not just participants with low weight and/or diminished skeletal muscle mass, which is typically associated with frailty, providing further evidence that the 'typical frailty patient' does not exist.

Subjective clinician estimates of frailty are inherently biased and have been referred to as 'the new cloak of ageism', whereby some patients may be deemed 'too frail' for intervention (29). A relatively new term 'frailtyism' (i.e., prejudice, stereotyping, or discrimination based on the presence of frailty) has also been introduced (13). The ongoing use of unreliable subjective estimates of frailty could enable frailtyism to occur more frequently and could even result in potential legal ramifications if treatment delays or advancement of inappropriate treatment, based on incorrect identification of frailty, were to occur (13). If a frailty assessment is being used to determine suitability for further clinical intervention, a clinician estimate would not be sufficient, as evidenced by our results.

Furthermore, frailty assessment allows much more than a classification of frailty status; it guides clinicians in selecting the most appropriate candidates for high-risk, costly, and finitely resourced cardiac interventions. With greater numbers of older, more complex heart failure patients, careful patient selection and correct identification of frailty is increasingly important (32).

The results of FRAME-HF Study 2 suggest that subjective estimates of frailty have no place in the treatment of patients with heart failure. We acknowledge there is still work to do, namely, universally defining frailty, agreeing upon the optimal assessment method and a validated frailty instrument for use in patients with heart failure is urgently needed. Frailty, when correctly identified with an instrument, can be used as a highly sensitive and predictive risk-stratification tool, while subjective clinician estimates of frailty are vague and unreliable. Therefore, clinician estimates of frailty and other informal subjective frailty

identification methods should finally be made a thing of the past and formal frailty assessment put in its place. As Hubbard and Story (2015) so eloquently state: “an *end-of-the-bed* frailty assessment in which the patient stays in bed like a cardiologist not listening to the chest: fated to miss vital and informative clinical signs” (p.525) (29).

4.6.1 Strengths and limitations

This study is one of the first to compare clinician-estimated frailty to formal frailty assessment in patients with heart failure. These results provide justification for regular formal frailty assessment in patients with heart failure, not subjective clinician estimates of frailty. Some limitations must be noted. This study was a single-centre analysis with a limited sample size. People with diagnosed dementia or cognitive illness that prevented them from providing informed consent and those who were non-English speaking were excluded, which is a significant limitation of the study.

4.7 Conclusion

Subjective clinician-estimated frailty did not show strong correlation or agreement to formal frailty assessment in this cohort of adults with heart failure. This study confirms the vital importance of conducting a formal frailty assessment in patients with heart failure, rather than an ‘*end-of-the-bed*’ or ‘*eyeball*’ frailty assessment, underscoring the need for assessment using a valid and reliable instrument. The adoption of routine formal frailty assessment in the clinical setting and the validation of a universally accepted frailty instrument for use in patients living with heart failure should be a high priority for future research.

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Chapter 5: Evaluating the validity of frailty assessment instruments potentially relevant for use in adults with heart failure: a prospective cohort study

5.1 Preamble

Frailty, as a syndrome with clinical relevance to the clinical outcomes and wellbeing of adults living with heart failure, was established in Chapter 1. While the next Chapter identified an absence of consensus regarding the 'optimal' frailty instrument for use in adults living with heart failure, it also noted that there had been a focus on the use of physical frailty instruments in heart failure studies. As a result, there is no robust evidence to support if this is the most suitable approach for a heart failure population. The mixed methods design of the FRAME-HF project was described in Chapter 3. The second of three studies was presented in Chapter 4, which compared clinician estimates of frailty and to a formal frailty assessment in adults living with heart failure. This cross-sectional study found that clinician estimates of frailty were not a suitable replacement for assessment using a frailty instrument. This finding reinforces the recommendation that undertaking a routine formal frailty assessment is essential to identify the presence of frailty in people living with heart failure. These results provide the context and background for Study 3, which is presented in this Chapter; the FRAME-HF project's final study evaluating the validity of frailty instruments potentially relevant for use in people with heart failure. This study comprises of two parts:

- Part A focuses on the convergent and discriminant validity of three physical frailty instruments; and
- Part B focuses on the predictive performance of six common frailty instruments (three physical and three multi-domain instruments).

The results of Study 3- Part A were published in *The European Journal of Cardiovascular Nursing*, a copy of which is provided in Appendix 1; and the results of Part B have been submitted to the *International Journal of Nursing Studies* and are currently under review. To

avoid repetition for the reader, the combined methods of Study 3 were presented in Chapter 3. The results and discussion of Study 3 Part A and B are presented here.

5.2 Publication reference for Study 3 – Part A

This chapter section includes a slightly modified version of the published manuscript, which is referenced below. A copy of the full published manuscript is included in Appendix 1.

> **McDonagh J**, Salamonson Y, Ferguson C, Prichard R, Jha SR, Macdonald PS, Davidson PM, Newton PJ. Evaluating the convergent and discriminant validity of three versions of the frailty phenotype in heart failure: results from the FRAME-HF study. European Journal of Cardiovascular Nursing. 2019;19(1):55-63.
> [Impact factor 2.296] Citations: 3

5.3 Context for Study 3 – Part A

As previously described, frailty is a complex clinical syndrome associated with an increased vulnerability to acute stressors (1, 2). Frailty is strongly associated with heart failure and is a predictor of poor health outcomes, including hospitalisation and mortality (3, 4). Frailty and heart failure share common underlying pathophysiological mechanisms. Both are associated with higher levels of circulating inflammatory cytokines, and both exhibit common symptomatology of exhaustion and decreased exercise tolerance. Cognitive impairment, depression, sarcopenia and cachexia are also common in heart failure and frailty (5).

There is a high variation in the prevalence of frailty in heart failure ranging from 15-79%. This large range in prevalence rate may be due to a number of factors, including study population, the timing of assessment in the illness trajectory, and which instrument was used (6). To date, there are no validated frailty assessment instruments for use in people with heart failure; this could explain significant measurement heterogeneity, and hence, variability in classifications of frailty. A recent systematic review identified seven frailty instruments that have been utilised in heart failure studies (6). As identified in Chapter 2, the most commonly used instrument was the Frailty Phenotype, which defines frailty as a syndrome of increased vulnerability to acute stressors, causing age-related physical decline (2, 6). Despite being frequently used to assess frailty in people with heart failure, this instrument's validity for use in people living with heart failure has yet to be determined. There are also many modified versions of the Frailty Phenotype which have been used in heart failure studies, but the validity of these modifications is also unclear (6).

To date, there has been a focus on physical frailty in heart failure studies (6). Therefore, this study sought to focus on evaluating the validity of physical frailty instruments in the first instance and aimed to provide evidence of the convergent and discriminant validity of three different versions of the Frailty Phenotype in adults with heart failure: the original Frailty Phenotype (2), the SHARE-FI (7) and the SVF (8), which are all measures of physical frailty. We hypothesised that in this cohort, those classified as frail would also score poorly in other physical and psychosocial sub-constructs specific to heart failure such as depression, poor physical performance and low quality of life. (9-11).

5.4 Methods - Part A

As outlined in Chapter 3, sociodemographic and clinical data were collected baseline, along with frailty, which was assessed using the Frailty Phenotype, the SVF and the SHARE-FI.

5.4.1 Statistical analyses

Demographic and clinical characteristics were summarised using descriptive statistics; continuous data were summarised using means ± standard deviation for normally distributed data or median (inter-quartile range) for non-parametric data. Categorical variables were summarised using frequencies and percentages. For the group comparisons, the one-sample Kolmogorov-Smirnov test indicated that none of the continuous variables were normally distributed; these variables were dichotomised at the median (12). Pearson's correlation coefficient was used to examine convergent validity and the chi-square test for discriminant validity. The threshold for statistical significance was a *p*-value of <0.05.

5.5 Results – Part A

A total of 131 adults living with heart failure ('participants') were recruited and included in the analyses. Over three quarters (76%) were male, with a mean age of 54 ± 14 years. Two-thirds (65%) were inpatients, with the majority of those admitted for heart failure-related causes (93%). The majority reported English as their first language (94%), and three-quarters (76%) were of Caucasian background (Refer Table 5-1).

Table 5-1 Baseline characteristics.

Baseline characteristics N = 131	N (%), Mean ±SD, Median (IQR)
Age (years)	54 ± 14
Sex (male)	99 (76)
Inpatient	83 (65)
Length of stay days of inpatients	20 (12-35)
Caucasian background	100 (76)
English language	123 (94)
Heart failure related hospitalisation	77 (93)
Medical history and clinical characteristics	
LVEF	31 ± 16
Myocardial infarction	32 (24)
Atrial fibrillation	70 (53)
Stoke	14 (11)
Hemiplegia	3 (2)
Chronic respiratory disease	18 (14)
Biochemistry	
Haemoglobin (g/L)	129 ± 25
Estimated Glomerular Filtration Rate (mL/mn/1.73m2)	62 ± 21
Creatinine (umol/L)	108 (88-136)
Medications	
Beta-blocker	78 (66)
RAAS inhibition	97 (74)
Loop diuretic	103 (77)
Anticoagulants	76 (59)
Antiarrhythmic	48 (38)
Vitamin D	20 (16)
Physical and psychosocial characteristics	
Kilocalories expended per week (n= 131)	.00 (.00-129)
Left hand grip strength (Kgs) (n= 128)	30 ± 29
Right hand grip strength (Kgs) (n= 129)	30 ± 12
Five-metre walk speed (secs) (n= 116)	5.1 ± 4.5
MoCA score (n= 114)	26 ± 3
DMI-10 (n= 123)	3 (1-12)

Key: LVEF; Left ventricular ejection fraction, RAAS; Renin angiotensin aldosterone system, MoCA; Montreal Cognitive Assessment, DMI-10; Depression in Medical Illness-10.

5.5.1 Frailty prevalence

The frailty prevalence rates varied across the three instruments, ranging from 33-54% classified as frail, 31-54% classified as pre-frail and 1-19% classified as non-frail (Refer Figure 5.1).

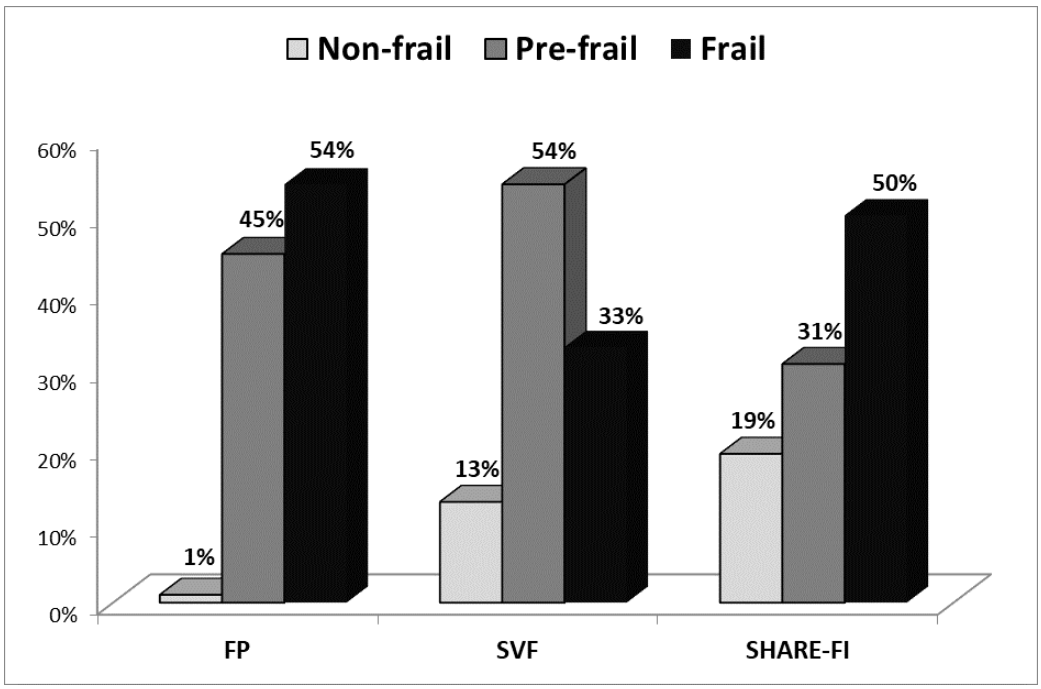

Figure 5-1 Frailty classification according to three physical frailty instruments.

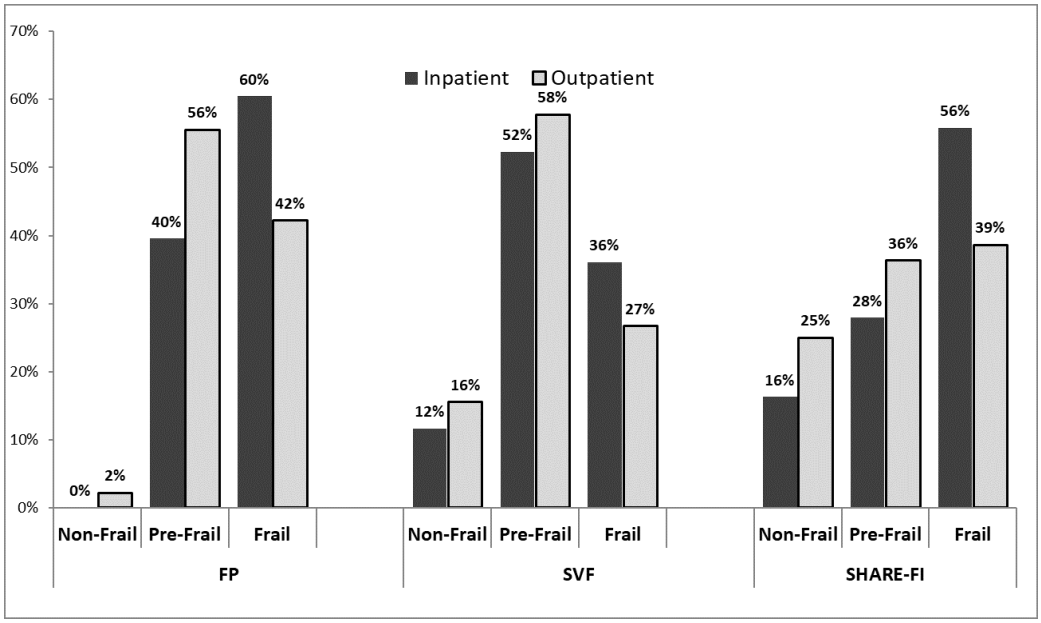

Figure 5-2 Frailty classifications of inpatients and outpatients according to instrument.

Key: FP, Frailty Phenotype; SHARE-FI, Survey of Health, Ageing and Retirement in Europe Frailty Instrument; SVF, St Vincent's Frailty Instrument.

There was a statistically significant difference between the prevalence of frailty between inpatients and outpatients (Refer Figure 5-2). Of the five frailty domains measured according to the three instruments, the 'weight loss/poor appetite' domain was the most consistent across the Frailty Phenotype, SVF and SHARE-FI instruments, with 41%, 53%, and 49% of the cohort positive in this domain respectively. The 'slowness' domain was the least consistent with the Frailty Phenotype and SVF, reporting that 15% and 27% were positive and the SHARE-FI reporting 77% positive in this domain. According to the SHARE-FI and SVF, 34% were positive in the 'physical inactivity domain', while 86% were positive in this domain according to the Frailty Phenotype (Refer Figure 5-3).

Analysis of the five frailty domains according to inpatient or outpatient status revealed there was a statistically significant difference between those positive in the 'physical inactivity' domain of the Frailty Phenotype (90% inpatients, 78% outpatients, p= 0.041) and between inpatients and outpatients who were positive in the 'slowness' domain of SVF (34% inpatients, 13% outpatients, p= 0.012) (Refer Table 5-2)

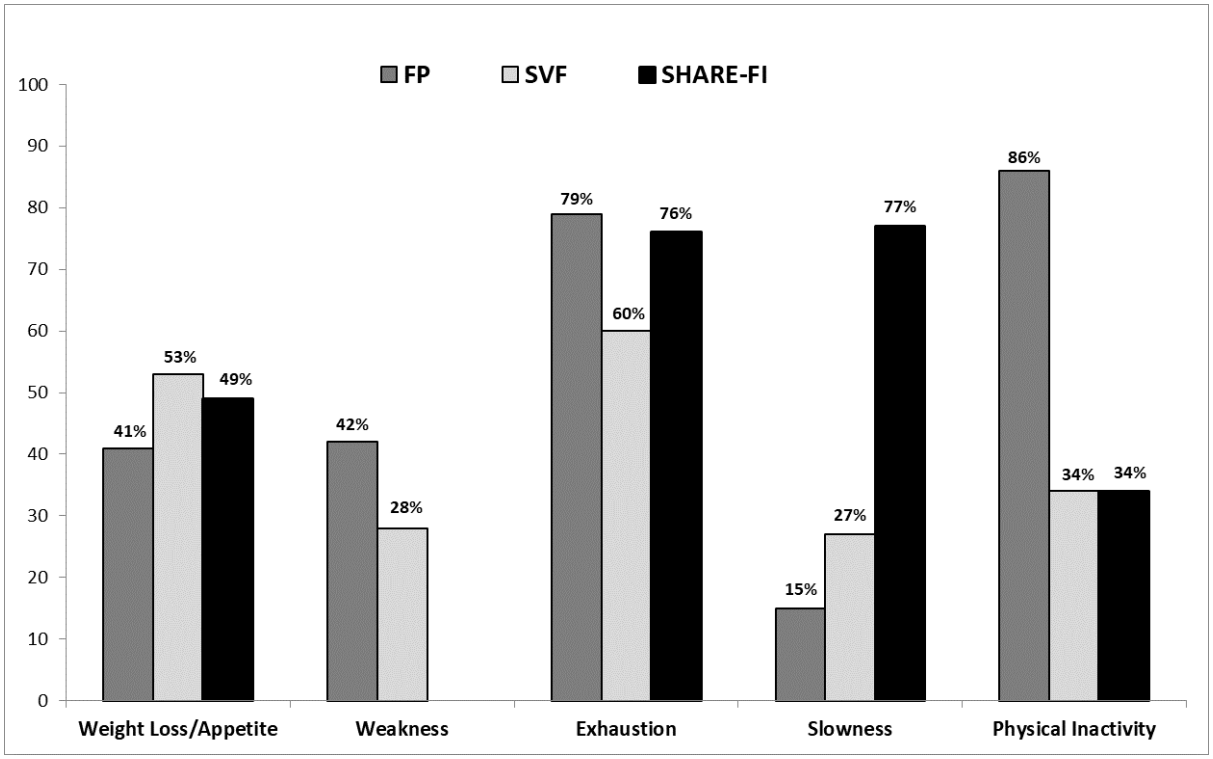

Figure 5-3 Proportion of participants classified as positive in the five frailty domains according to frailty instrument.

Key: FP, Frailty Phenotype; SHARE-FI, Survey of Health, Ageing and Retirement in Europe Frailty Instrument; SVF, St Vincent's Frailty Instrument.

Table 5-2 Proportion of inpatients and outpatients classified as positive in the five frailty domains according to instrument.

	Weight loss / appetite			Weakness			Exhaustion			Slowness			Physical inactivity		
	n (%)	X^2 (df=1)	p-value	n (%)	X^2 (df=1)	p-value	n (%)	X^2 (df=1)	p-value	n (%)	X^2 (df=1)	p-value	n (%)	X^2 (df=1)	p-value
FP	37 (43)	0.470	0.465	38 (44)	0.158	0.691	67 (80)	0.271	0.603	15 (17)	1.400	0.237	78 (90)	4.161	0.041*
	16 (36)			17 (42)			36 (82)			4 (10)			35 (78)		
SVF	48 (56)	0.569	0.451	25 (29)	0.317	0.573	51 (59)	0.006	0.938	29 (34)	6.272	0.012*	28 (33)	0.119	0.730
	22 (49)			11 (24)			27 (60)			6 (13)			16 (36)		
SHARE-FI	44 (51)	0.379	0.538				70 (81)	2.863	0.091	69 (80)	0.946	0.331	28 (33)	0.119	0.730
	20 (46)						30 (67)			32 (73)			16 (36)		

*Key: FP, Frailty Phenotype; SHARE-FI, Survey of Health, Ageing and Retirement in Europe Frailty Instrument; SVF, St Vincent's Frailty Instrument. X2= Chi Square; df= degrees of freedom; *Indicates statistical significance, ^Unable to calculate as the variable is kept continuous*

5.5.2 Convergent Validity

The correlations between the versions were highest between SHARE-FI and the SVF (*r* = 0.64, *p* = <0.001), followed by between SVF and Frailty Phenotype (*r* = 0.51, *p* = <0.001), and finally between SHARE-FI and Frailty Phenotype (r = 0.45, p = <0.001). The NYHA classes were moderately correlated with SVF (*r* = 0.47, p = <0.001), SHARE-FI (*r* = 0.42, p = <0.001) and the Frailty Phenotype (r = 0.42, p = <0.001). Similarly, the AKPS scores were also low to moderately correlated with all three versions: SVF (r = 0.43, p = <0.001), SHARE-FI (r = 0.39, p = <0.001) and Frailty Phenotype (r = 0.24, p = <0.001). All EQ-5D-5L dimensions were low to moderately correlated with each of the versions except for the anxiety and depression dimension, which was only correlated with the SVF. The DMI-10 and the MoCA score were also only correlated with the SVF.

5.5.3 Discriminant Validity

Statistically significant group differences were detected between normal and abnormal AKPS, EQ5D-5L and DMI-10 scores within the three frailty categories (not-frail, pre-frail and frail) according to SVF and SHARE-FI. The Frailty Phenotype was only able to detect statistically significant group differences between normal and abnormal AKPS scores (Refer Table 5-3). Both the Frailty Phenotype (60% vs 42%; p= 0.067) and SHARE-FI (56% vs 39%; p= 0.170) were able to discriminate between inpatients and outpatients who were classified as frail (Refer Figure 5-2).

Table 5-3 Group comparison analysis of each frailty instrument and abnormal scores of the heart failure related sub-construct assessments.

Clinical Characteristics	Frailty category	FP (%)	X^2 (df =2)	*P* value	SVF (%)	X^2 (df =2	*P* value	SHARE-FI (%)	X^2 (df =2	*P* value
Charlson Index score (> 2)	Frail	60	3.151	0.207	40	2.374	0.305	*60*	5.379	0.068
	Pre-frail	38			50			28		
	Non-frail	2			10			12		
MoCA score (Up to 26)	Frail	57	1.535	0.464	33	0.976	0.614	48	0.214	0.899
	Pre-frail	42			58			31		
	Non-frail	2			9			21		
AKPS score (Up to 70)	Frail	61	10.094	0.006*	40	11.066	0.004*	57	9.249	0.010*
	Pre-frail	40			50			28		
	Non-frail	1			11			16		
DMI-10 score (≥9)	Frail	60	1.296	0.523	37	7.327	0.026*	50	7.871	0.020*
	Pre-frail	40			63			44		
	Non-frail	0			0			6		
EQ5D-5L VAS (Up to 60)	Frail	60	3.415	0.181	48	17.910	<0.001*	60	7.322	0.026*
	Pre-frail	40			40			28		
	Non-frail	0			12			13		

*Note: Pearson chi-squared, indicates statistically significant * Key: FP, Frailty Phenotype; SHARE-FI, Survey of Health, Ageing and Retirement in Europe Frailty Instrument; SVF, St Vincent's Frailty Instrument; MoCA- Montreal Cognitive Assessment, AKPS- Australia-Modified Karnofsky Performance Scale, DMI-10, Depression in Medical illness-10, EQ5D-5L- EuroQoL5D-5L Visual Analog Score*

5.6 Discussion – Part A

This study of three physical frailty instruments in adults living with heart failure showed that measurement heterogeneity exists within the same cohort, even when measuring the same frailty domains. Previous reviews of frailty in heart failure have reported large variance in the prevalence rate, and this difference is likely due not just to study design and population but to the frailty instrument chosen (13, 14). As this study has demonstrated, when using different versions of the same instrument, even minor modifications provide vastly different results. It is therefore important that studies identify not only the instrument used but also if a modified version has been used and any validation work of the modified instrument that was undertaken.

This study revealed that most of the frailty domains across the three instruments were highly variable. The weight loss/appetite domain was the most consistent across the three instruments. The Frailty Phenotype uses a question related to a weight loss of 'more than 5kg of unintended weight loss in the previous 12 months', the SVF and SHARE-FI both use a question related to appetite. In this study, replacing the weight loss question with a question regarding appetite did not significantly alter the outcome in this domain and so would seem to be appropriate, particularly given the challenges of accurately assessing self-reported, unintended weight loss in heart failure. The slowness and physical inactivity domains displayed a floor and ceiling effect in each instrument, and therefore may not be appropriate at capturing those with heart failure who are positive in these frailty domains.

The slowness domain was the least consistent across the five frailty domains with 15%, 27% and 77% positive in this domain according to the Frailty Phenotype, SVF and SHARE-FI, respectively. The five-metre walk test is used to measure slowness in the Frailty Phenotype and SVF, but the result is calculated differently for both. There were 11% of the cohort who were unable to complete the five-metre walk test. The majority of these were due to the patient being too unwell and, therefore, unable to mobilise to perform the test. For analysis, those unable to complete the five-metre walk test were given a point and assessed as positive in this domain. While walking speed as a measure of physical function has been used clinically across many health conditions, there is no advice guiding when it is clinically advisable for a person with heart failure to mobilise or refrain from attempting this test (8, 15, 16). The clinical boundaries around performing the five-metre walk test in heart failure

need to be established. There were also significant differences detected between inpatients and outpatients who were positive in this domain according to the SVF (34% vs 13%, p= 0.012) but not with the Frailty Phenotype (17% vs 10%, p= 0.237). The SHARE-FI replaces the five-metre walk speed test with two questions related to an individual's ability to walk 100 metres or climb a flight of stairs without resting. While less burdensome for a participant to complete, this replacement question is subjective, and the ambiguous timeframe may cause individuals to over or underestimate their abilities. The SHARE-FI slowness questions are also closely related to exercise capacity, which may be problematic in those with heart failure. With decreased exercise tolerance and shortness of breath intrinsic to heart failure (17), asking someone with symptomatic heart failure if they have difficulty walking 100 metres or climbing a flight of stairs, they are likely to respond 'yes', which could explain why 77% were positive in this domain according to the SHARE-FI. The benefit of the five-metre walk speed test is that it allows the assessment of walking speed over a short distance. Those with heart failure will likely start a walking speed test at their normal pace but have to slow down or stop before they reach one hundred metres. Therefore, the five-metre walk speed test may provide better discrimination between slowness caused by frailty and slowness caused by heart failure.

To assess physical inactivity, the Frailty Phenotype uses a 12-item shortened instrument of the Minnesota Leisure Time Activity Questionnaire, which asks the participant to recall the amount of time spent performing physical activities over the last two weeks, such as walking for exercise, jogging and tennis (18). As more than two-thirds of our cohort were inpatients, many of whom were in hospital for greater than two weeks at the time of assessment, it was difficult for participants to answer the questions, as most pertain to physical activities performed outside, making it impossible for people to complete these activities while hospitalised. We had responses from all participants, but only 45% of the cohort answered that they had completed any of the physical activities listed on the Questionnaire. Therefore, we were unable to calculate a mean Kcals expenditure per week result greater than 0. Consequently, 86% were positive in the physical inactivity domain according to the Frailty Phenotype (90% inpatient vs 78% outpatient p= 0.041). These results suggest that the Minnesota Leisure Time Activity Questionnaire has poor utility in heart failure, particularly in those who are hospitalised. There may be scope in future research to explore if modifying

the activities listed may be more appropriate in heart failure or if wearable physical activity trackers could be more useful (19).

This study showed that the two modified versions of the Frailty Phenotype, the SVF and the SHARE-FI, displayed stronger validity than the original Frailty Phenotype. The SVF instrument correlated most highly to the other relevant heart failure sub-constructs, displaying good convergent validity. The SHARE-FI also displayed good convergent validity with low to moderate correlation with the sub-constructs assessed.

The SHARE-FI and SVF both displayed discriminant validity, with both instruments able to detect significant group differences between the three frailty classifications (not-frail, pre-frail and frail) and abnormal scores in three out of five of the heart failure-related sub-constructs. The Frailty Phenotype was only able to detect significant group differences in one out of five sub-constructs. The SHARE-FI was also able to discriminate between the inpatients and outpatients who were classified as frail; it was able to recognise that (as expected) those who were admitted to hospital at the time of frailty assessment had higher rates of frailty than those who were outpatients.

Strengths and Limitations

The strengths of Study 3 Part A include the pragmatic design, which aims to improve the clinical applicability of these results in the hope of standardising methods of assessment and interpretation. Some limitations also need to be considered. First, the sample we used is unique compared to other heart failure studies and may limit the generalisability of results; it was a younger cohort, reflecting the population of the study site, and the length of stay for those that were inpatients was considerably higher compared to other heart failure studies (20, 21). The high prevalence of frailty in those with heart failure, despite the low mean age, is further evidence of the strong association between frailty and heart failure.

Implications for practice

This study provides information regarding the convergent and discriminant validity of three physical frailty instruments in those with heart failure. These results highlight the variability of frailty prevalence between instruments (even when using different versions of the same frailty instrument). It is important that studies assessing frailty identify not only the instrument used, but if any modifications have been made, as even minor modifications to a frailty instrument can cause variations in prevalence rates.

5.7 Summary – Part A

The SVF and SHARE-FI both displayed adequate convergent and discriminant validity, suggesting both instruments are valid measures of frailty in those with heart failure. To the authors' knowledge, this is one of the first studies to compare the validity of different physical frailty instruments in people with heart failure. These results need to be confirmed in a larger and more diverse heart failure cohort.

5.8 Publication reference for Study 3 – Part B

This chapter section contains a slightly modified version of a submitted manuscript currently under review in a Q1 journal.

McDonagh J, Ferguson C, Prichard R, Chang S, Phillips JL, Davidson PM, Macdonald PS, Newton PJ. Predictive performance of six frailty instruments in adults with heart failure: 12-month outcomes from the FRAME-HF study.2021; The International Journal of Nursing Studies (Under Review).

5.9 Context for Study 3 – Part B

To date, there has been a focus on physical frailty instruments and domains when assessing frailty in people living with heart failure, with the Frailty Phenotype, which focuses on five physical domains of frailty, identified as the most commonly used instrument in heart failure studies (2, 6) However, there is an absence of consensus as to whether physical frailty instruments are the most suitable choice for this population (6, 22, 23). Heart failure, particularly in the advanced stages, can have profoundly negative effects on physical functioning, therefore, focusing on physical frailty domains may be inappropriate and contribute to an over or under estimation of frailty (17). A proposed alternative to physical instruments are multi-domain frailty instruments. Multi-domain instruments define frailty as a multidimensional syndrome capable of triggering decline in various domains of human functioning, rather than just physical, comprising the assessment of multiple frailty domains (5, 22). Some multi-domain instruments can be completed with routinely collected medical record data, eliminating the need for objective physical measures (24). The most widely used multi-domain instrument is the Deficit Accumulation Index developed by Rockwood and colleagues which categorizes frailty based on the number of functional deficits an individual has (25).

There has been limited head-to-head comparison of the predictive performance of multiple frailty instruments in adults living with heart failure. Thus, there is no consensus on how best to assess frailty in this population. Study 3 Part A presented an evaluation of three physical frailty instruments convergent and discriminant validity, revealing that the SHARE-FI and the SVF displayed stronger convergent and discriminant validity than the Frailty Phenotype (26). Study 3 Part B is a logical next step and aims to provide information

regarding the predictive ability of both physical and multi-domain frailty instruments to inform future practice on how best to assess frailty in adults with heart failure.

5.10 Methods – Part B

A detailed overview of the methods was provided in Chapter 3. A brief description of the study measures used, and the analyses undertaken is provided here.

Frailty was assessed using six frailty instruments: three physical instruments, the Frailty Phenotype, the SHARE-FI, and the SVF; and three multi-domain instruments, the SVF plus cognitive and mood items (SVF+), the Fatigue, Resistance, Ambulation, Illnesses, & Loss of Weight (FRAIL) scale, and the Deficit Accumulation Index.

The Frailty Phenotype, SVF and the SHARE-FI are all based on Fried's five physical domains of frailty: weakness, unintentional weight loss (shrinkage), physical inactivity, slowed walking speed, and exhaustion (2, 8, 27). Individuals are classified as frail if positive in three or more of the five domains (with the exception of the SHARE-FI, which calculates frailty based on an algorithm) (27). The SHARE-FI and SVF replace unintentional weight loss with poor appetite, which may be more appropriate for a heart failure population (26).

The Deficit Accumulation Index assesses frailty through the accumulation of deficits, the more deficits a person has, the more frail they are (25). A Deficit Accumulation Index was created comprising 31 deficits; these were selected based on previously published criteria and included deficits relevant to frailty and heart failure (28-30). The Deficit Accumulation Index was calculated using data collected at baseline, including the Charlson comorbidity index (31), medical history, NYHA class, functional status, psychosocial health, pathology results and mobility (Appendix 5). The Deficit Accumulation Index is calculated by dividing the number of deficits present by the number of deficits assessed, giving a score from 0 -1; that is, if a patient exhibited 5/31 deficits, their frailty index score was 0.16 (30). For the purpose of this analysis, frailty was defined as a score of > 0.25, which has been suggested by Rockwood as a suitable cut-off point (32, 33).

The FRAIL scale is a multi-domain frailty instrument developed and validated by Morley and colleagues (24). The five-item scale scores people across the following domains: fatigue, resistance, ambulation, number of illnesses and loss of weight. One point is given for each component: a score of 3-5 represents frail; 1-2 represents pre-frail; and a score of zero

represents robust (or non-frail) (24). The FRAIL Scale was selected as it does not require any objective physical measures and includes domains related to comorbidities, which is pertinent to both frailty and heart failure (5).

The SVF+ (34) consists of the same items as the SVF instrument plus cognition, as assessed by the Montreal cognitive assessment (MoCA) version 7.1 (35) and mood, as assessed by the Depression in medical illness 10 questionnaire (DMI-10) (36). Positive in three or more of the seven domains was classified as frail, 1- 2 was pre-frail, and zero was non-frail (34).

5.10.1 Statistical analyses

All frailty instruments were analysed using a dichotomous variable: frail or non-frail. Baseline socio-demographic and clinical characteristics were summarised using descriptive statistics stratified into frail and non-frail according to the six frailty instruments. Continuous data were summarised using means ± standard deviation and compared using the analysis of variance test (ANOVA). Categorical variables were summarised using frequencies and percentages and compared using the chi-squared test. A p-value of < 0.05 was the threshold for statistical significance.

Multiple logistic regression was used to create six frailty instrument models, which evaluated the association between each frailty instrument and all-cause rehospitalisation and mortality at 12-months, adjusting for potential confounding factors (age, sex, eGFR, and albumin). The predictive performance of each frailty instrument model was also compared by plotting receiver operating characteristic (ROC) curves and calculating C-statistic values (area under the curve). The C-statistic indicates how good a model is at correctly classifying outcomes, with a value of >0.70 considered acceptable discrimination (37, 38).

5.11 Results – Part B

The sample comprised 131 adults with a mean age of 54 (± 14) years old. Seventy-six per cent were male, and most had mild/moderate heart failure symptoms with NYHA class II and III (80%). The baseline characteristics stratified by frail and non-frail according to each instrument were analysed, the SHARE-FI and the Deficit Accumulation Index displayed the greatest discrimination between the ‘frail’ and ‘non-frail’ groups. (Refer Table 5-4).

Table 5-4 Baseline characteristics of participants stratified by 'frail' and 'non-frail' according to six frailty instruments.

		Frailty Phenotype (2)			SHARE-FI (27)			St Vincent's Frailty instrument (8)			St Vincent's Frailty plus cognition and mood (34)			The FRAIL Scale (24)			Deficit Accumulation Index (25)		
	All (N=131)	Non-Frail (N=60)	Frail (N=71)	P Value	Non-Frail (N=65)	Frail (N=65)	P value	Non-Frail (N=88)	Frail (N=43)	P value	Non-Frail (N=54)	Frail (N=77)	P Value	Non-Frail (N=56)	Frail (N=74)	P value	Non-Frail (N=25)	Frail (N= 103)	P value
Age (years)	54 ± 14	53 ± 16	54 ± 13	0.502	52 ±16	56 ± 12	0.183	52 ± 15	58 ± 11	0.023*	51 ± 15	56 ± 14	0.085	49 ± 16	58 ± 11	<0.000 *	41 ± 17	57 ± 12	<0.00 0*
Sex (Male), n (%)	99 (76)	51 (85)	48 (68)	0.021*	50 (77)	48 (74)	0.684	66 (75)	33 (77)	0.827	40 (74)	59 (77)	0.738	44 (77)	54 (73)	0.463	19 (76)	78 (76)	0.977
BMI (kg/m^2) *a*	27 ± 6	28 ± 6	27 ± 5	0.086	27 ± 6	28 ± 5	0.575	28 ± 6	26 ± 5	0.190	28 ± 6	27 ± 5	0.785	27 ± 6	26 ± 6	0.658	26 ±7	28 ± 5	0.141
Charlson Index	3 ± 2	2 ± 1	3 ± 2	0.090	2 ± 1	3 ± 2	0.016*	2 ± 2	3 ± 2	0.065	2 ± 1	3 ± 2	0.019*	2 ± 1	3 ± 2	0.0098	2 ± 1	3 ± 2	0.001 *
LVEF *b*	31 ± 16	31 ± 16	30 ± 16	0.814	31 ± 18	30 ± 15	0.624	30 ± 17	32 ±16	0.389	29 ± 15	32 ± 17	0.235	31 ± 18	30 ± 16	0.609	31 ± 19	30 ± 16	0.758
NYHA III-IV, n (%)	NYHA I – 12 (9) NYHA II – 44 (34) NYHA III – 61 (47) NYHA IV – 14 (11)	23 (38)	52 (73)	<0.000 *	26 (40)	48 (74)	<0.000 *	35 (40)	40 (93)	<0.000 *	20 (37)	55 (71)	<0.000 *	19 (34)	55 (74)	<0.000 *	7(28)	66 (64)	0.001 *
MoCA ≤26, n (%) *a*	57 (44)	22 (37)	35 (50)	0.171	29 (46)	64 (100)	0.796	36 (42)	21 (50)	0.384	10 (19)	47 (62)	<0.000 *	24 (44)	33 (46)	0.805	10 (42)	46 (46)	0.731
DMI ≥9, n (%) *c*	38 (29)	14 (23)	24 (34)	0.209	29 (46)	19 (30)	0.890	24 (28)	14 (33)	0.558	5 (9)	33 (43)	<0.000 *	11 (20)	26 (35)	0.060	5 (20)	30 (29)	0.345

AKPS score	65 ± 14	70 ± 12	60 ± 14	<0.000*	70 ± 12	59 ± 15	<0.000*	69 ± 13	55 ± 13	<0.000*	72 ± 12	59 ± 14	<0.000*	72 ± 12	59 ± 14	<0.000*	70 ± 13	63 ± 15	0.020*
Hgb (mg/L) ***d***	129 ± 24	133 ± 28	126 ± 22	0.091	135 ± 28	122 ± 20	0.005*	133 ± 26	122 ± 20	0.019*	130 ± 30	128 ± 21	0.505	136 ± 28	124 ± 21	0.006*	147 ± 23	125 ± 24	<0.000*
eGFR (mL/min) ***a***	62 ± 21	66 ± 21	59 ± 21	0.088	66 ± 21	58 ± 20	0.022*	66 ± 20	54 ± 20	0.002*	67 ± 19	59 ± 22	0.022*	70 ± 20	56 ± 20	<0.000*	72 ± 19	60 ± 21	0.008*
Albumin (mg/L) ***d***	40 ± 6	42 ± 4	39 ± 7	0.015*	41 ± 5	39 ± 7	0.058*	40 ± 6	40 ± 5	0.787	40 ± 7	40 ± 5	0.917	41 ± 16	39 ± 7	0.038	41 ± 4	40 ± 6	0.229
Drugs > 5, n (%)	108 (82)	48 (80)	60 (85)	0.499	48 (74)	64 (100)	0.005*	68 (77)	40 (93)	0.026*	45 (83)	63 (82)	0.822	42 (75)	66 (89)	0.033*	15 (60)	92 (89)	<0.000*

Key: BMI, Body Mass index; LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association Class; MoCA, Montreal Cognitive Assessment; DMI-10, Depression in Medical Illness; AKPS, Australian Modified Karnofsky Score; Hgb, Haemoglobin; eGFR, Estimated glomerular filtration rate. Denotes statistically significant. The SHARE-FI and FRAIL scale were only available in 130 participants, and the Deficit Accumulation Index was only available in 127 participants. a BMI, MoCA and eGFR was available in 128 participants, b LVEF was available in 129 participants, c DMI was available in 130 participants, d Hgb and albumin was available in 127 participants.*

5.11.1 Frailty prevalence

The prevalence of frailty varied widely across the different instruments (Refer Figure 5-4). Frailty prevalence, according to the physical frailty instruments, ranged from between 33% (SVF) and 54% (Frailty Phenotype). The multi-domain instruments reported a higher prevalence of frailty ranging from 57% (FRAIL scale) to 81% (Deficit Accumulation Index).

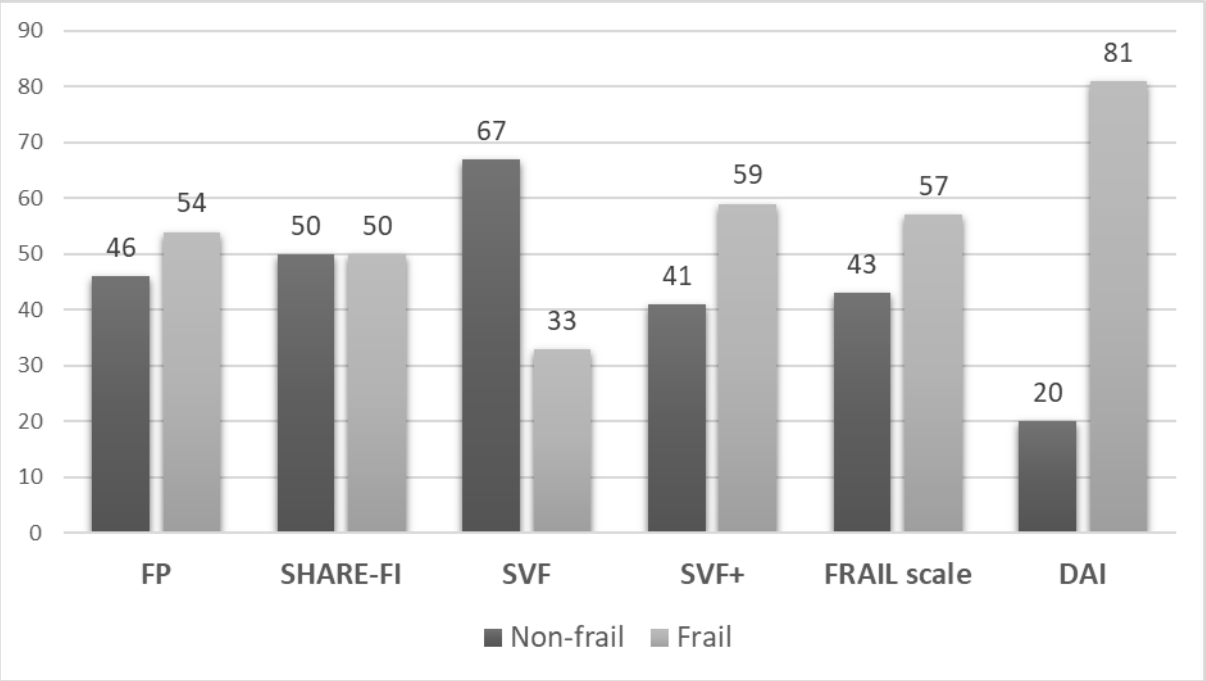

Figure 5-4 Frailty prevalence according to the six frailty instruments (%).

Key: FP, Frailty Phenotype; SHARE-FI, Survey of Health, Ageing and Retirement in Europe Frailty Instrument; SVF, St Vincent's Frailty Instrument; SVF +, St Vincent's Frailty Instrument plus cognitive and mood domains; FRAIL scale, Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight scale; and DAI, Deficit Accumulation Index.

5.11.2 All-cause rehospitalisation and mortality

A total of 83 participants (63%) experienced the composite outcome of rehospitalisation and/or mortality within the 12-month follow-up period. Over half (n=72, 55%) of participants were rehospitalised, 16% (n=21) died within the 12 months, and four were lost-to-follow-up. When stratified by frailty classification (frail or non-frail) and instrument, the outcomes were diverse. The Frailty Phenotype, SHARE-FI, and Deficit Accumulation Index all detected a significant difference in the number of composite events between the frail and non-frail group (p= 0.011; p= 0.011; and p= 0.005 respectively). The Deficit Accumulation Index classified 100% (n= 21) of deaths in the frail group and zero deaths in the non-frail

group (p= 0.014), and also the highest rate of rehospitalisation in the frail group compared to the non-frail group (n=62, 87% vs n= 9, 13%; p= 0.029). The Frailty Phenotype also identified a significant difference in the rate of rehospitalisation between the frail and non-frail group (n= 45, 63% vs n= 27, 38%; p= 0.035) (Refer Table 5.5).

Table 5-5 Twelve-month event outcomes stratified by frailty instrument.

		FP	SHARE-FI	SVF	SVF+	FRAIL scale	DAI
Composite rehospitalisation and mortality n= 83							
Non-frail, n (%)		31 (37)	34 (41)	52 (63)	31 (37)	30 (36)	10 (12)
Frail, n (%)		52 (62)	48 (58)	31 (37)	52 (63)	52 (63)	72 (87)
P-value		0.011	0.011	0.147	0.236	0.051	0.005
Mortality n= 21							
Non-frail, n (%)		7 (33)	7 (33)	11 (52)	7 (33)	7 (33)	0
Frail, n (%)		14 (67)	14 (67)	10 (48)	14 (67)	14 (67)	21 (100)
P-value		0.211	0.095	0.115	0.423	0.325	0.014
Rehospitalisation n= 72							
Non-frail, n (%)		27 (38)	31 (44)	47 (65)	29 (40)	27 (38)	9 (13)
Frail, n (%)		45 (63)	40 (56)	25 (35)	43 (60)	44 (62)	62 (87)
P-value		0.035	0.113	0.609	0.808	0.202	0.029

Key: FP, Frailty Phenotype; SHARE-FI, Survey of Health, Ageing and Retirement in Europe Frailty Instrument; SVF, St Vincent's Frailty Instrument; SVF +, St Vincent's Frailty Instrument plus cognitive and mood domains; FRAIL scale, Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight scale; and DAI, Deficit Accumulation Index.

5.11.3 Predictive performance

The results of the multiple logistic regression are presented in Table 5-6. The continuous independent variables met the assumption of being linearly related to the logit, and each model passed the Hosmer and Lemeshow test (38). All instruments, except the FRAIL scale, were associated with increased odds of rehospitalisation and/or mortality, though these results were non-significant. The Deficit Accumulation Index (adjusted Odds Ratio [OR]: 2.43; 95% Confidence Interval [95% CI]: 0.81 – 7.24) and SHARE-FI (adjusted OR: 1.66; CI: 0.74 – 3.72) demonstrated the strongest association. The frailty instrument model with the highest sensitivity was the SVF+ (92%), followed by the FRAIL scale (90%), SHARE-FI (90%) and the SVF (90%). The FRAIL scale model had the highest specificity of 46%. All six frailty instrument models displayed acceptable discrimination with C-statistic values between

0.71- 0.73 (38), as shown in Table 3 and Figure 2. The Deficit Accumulation Index and SHARE-FI models reported the highest C-statistic value of 0.73.

Table 5-6 Predictive performance of the six frailty instrument models: results of logistic regression and area under the curve analysis.

	P value	Sensitivity (%)	Specificity (%)	Odds Ratio (95% CI)	C-statistic value
FP	0.26	88	43	1.60 (0.70 – 3.61)	0.72
SHARE-FI	0.22	90	41	1.66 (0.74 – 3.72)	0.73
SVF	0.68	90	39	1.20 (0.50 -2.88)	0.71
SVF+	0.66	92	36	1.22 (0.54 – 2.72)	0.71
FRAIL scale	0.94	90	46	0.97 (0.41 – 2.30)	0.72
DAI	0.11	88	38	2.43 (0.81 -7.24)	0.73

Note: All models adjusted for age, sex, eGFR and albumin.

Key: FP, Frailty Phenotype; SHARE-FI, Survey of Health, Ageing and Retirement in Europe Frailty Instrument; SVF, St Vincent's Frailty Instrument; SVF +, St Vincent's Frailty Instrument plus cognitive and mood domains; FRAIL scale, Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight scale; and DAI, Deficit Accumulation Index.

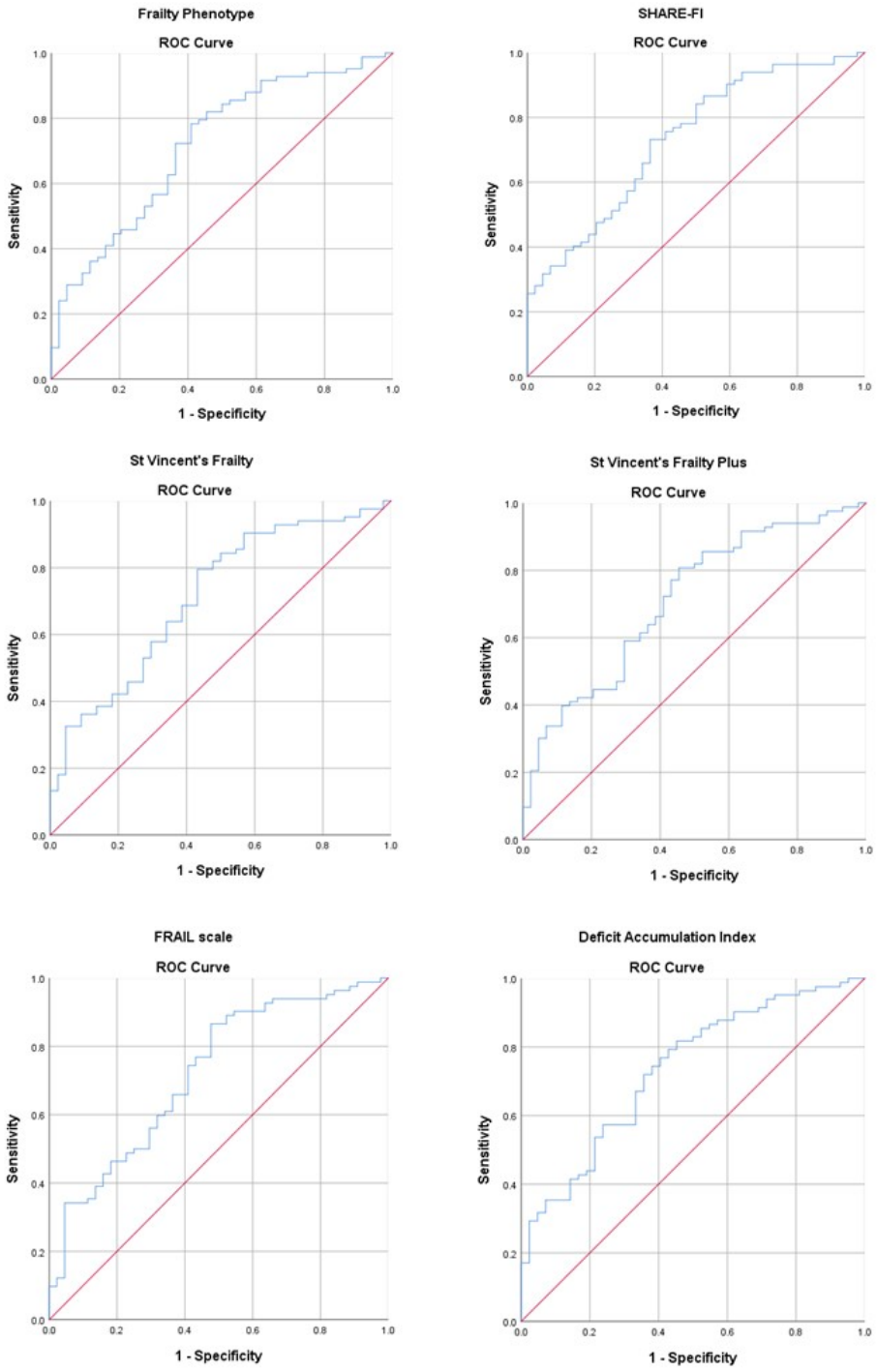

Figure 5-5 ROC curves for the six frailty instrument models

Key: FP, Frailty Phenotype; SHARE-FI, Survey of Health, Ageing and Retirement in Europe Frailty Instrument; SVF, St Vincent's Frailty Instrument; SVF +, St Vincent's Frailty Instrument plus cognitive and mood domains; FRAIL scale, Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight scale; and DAI, Deficit Accumulation Index.

5.12 Discussion – Part B

This study highlights the differences in the predictive performance of six frailty instruments in adults living with heart failure. The six instruments included in this study all performed similarly; all but one instrument (the FRAIL scale) was associated with increased odds of rehospitalisation and/or mortality. Overall discrimination of each frailty instrument model was satisfactory with C-statistic values between 0.71-0.73 and adequate sensitivity. While our results did not reach statistical significance, the Deficit Accumulation Index and SHARE-FI performed best overall, demonstrating the physical and multi-domain instruments were comparable in this cohort. These results also support McNallan et al. (2013) findings that a physical and multi-domain instrument (Deficit Accumulation Index and Frailty Phenotype) were equally able to predict mortality in adults with heart failure (n=233) (30).

Conversely, Testa et al. (2020) found that a multi-domain instrument performed better when comparing the Frailty Phenotype and a modified version of the Deficit Accumulation Index (29, 39) in a cohort of 1077 individuals aged >65 years (190 individuals with heart failure and 717 without heart failure) (22). In those with heart failure, the Deficit Accumulation Index was more predictive of mortality than the Frailty Phenotype (Hazard ratio (HR) 1.11 vs 0.63) and hospitalisation (HR 1.14 vs 1.03). They also reported higher C-statistic values in the Deficit Accumulation Index compared to the Frailty Phenotype for mortality (0.82 vs 0.63) and hospitalisation (0.81 vs 0.69) (22). The FRAME-HF cohort had slightly lower mortality rates and a similar rate of rehospitalisation as the heart failure patients in the Testa et al. study (22). However, the FRAME-HF results found no significant difference between the multi-domain and physical instruments, which may have been due to the smaller sample size or the much lower mean age of the cohort (54 vs 82 years) (22).

While the multi-domain and physical instruments were comparable in the FRAME-HF cohort, a recent meta-analysis by Yang et al. (2018) (3) reported the Frailty Phenotype had a higher estimate of hazard for mortality compared to the overall pooled (Frailty Phenotype/non-Frailty Phenotype) estimates (HR: 1.80 vs 1.54). Sze et al. (2019) also compared the Frailty Phenotype, Deficit Accumulation Index, and the multi-domain Edmonton Frail scale (40) in chronic heart failure (n= 467) (41). This study did not report on predictive ability, instead focusing on classification performance, showing the Frailty

Phenotype had higher sensitivity (93%) for identifying frailty than the Deficit Accumulation Index (75%) and Edmonton Frailty scale (62%).

The results of Study 3 Part B revealed the prevalence of frailty ranged from 33-81 % across the six instruments, strengthening the growing body of evidence regarding the heterogeneity of frailty prevalence in heart failure, even when instruments are well correlated or conceptually similar (13, 26, 41). For example, Sze et al. (41) reported frailty prevalence of 30-52% across three moderately correlated instruments (Frailty Phenotype, Deficit Accumulation Index and Edmonton Frail Scale) and only 26% of the cohort were assessed as frail by all three instruments. Moreover, the FRAME-HF results reveal that heterogeneity exists even when multiple instruments are measured concurrently and within the same cohort, reinforcing the need for a unified consensus of frailty definition and an optimal assessment instrument for heart failure (42).

The differences in frailty prevalence between the physical SVF and the multi-domain SVF+ are worth noting. Despite the two instruments displaying similar predictive ability, the prevalence of frailty increased from 33% (SVF) to 59% (SVF+). The SVF+ identifies a higher number of patients as frail; however, if the physical SVF was used, there would be a large number of patients missed or incorrectly identified as non-frail. When cognitive and mood domains were first added to the SVF instrument by Jha and colleagues (2016), the predictive ability of the instrument improved (34); while the FRAME-HF results did not reach statistical significance, they did reveal that the SVF+ had a marginally higher odds ratio for the composite endpoint compared to the SVF (OR: 1.22 vs 1.20).

All six of the frailty instrument models compared had high sensitivity but relatively low specificity. The FRAIL scale model had the highest specificity of 46% and a good sensitivity of 90%. However, the OR for this instrument was 0.97 (95% CI: 0.41 -2.43). The lack of association to the composite endpoint is most likely due to the smaller numbers. The FRAIL scale has been validated in middle-aged African American males (24). To the authors' knowledge, this is the first time it has been compared to other frailty instruments in those with heart failure. It was chosen for this study as it is brief, non-burdensome and does not require objective physical measures, which is an essential consideration for heart failure. The satisfactory balance between the FRAIL scale model's sensitivity and specificity suggests

it could be a suitable instrument for a heart failure population and thus warrants further investigation to evaluate its predictive ability and utility in this population.

The SHARE-FI was one of the strongest performers in this study, demonstrating association to the composite endpoint and good discrimination between the frail and non-frail groups in bivariate analyses. While not formally validated in heart failure, it has been validated in community-dwelling adults aged 50 or older (27) and has been utilised in heart failure studies before (20, 26, 43). The SHARE-FI offers a viable alternative to the Frailty Phenotype; it is quicker to administer and doesn't include a 'weight loss' domain or require completion of a five-metre gait speed test. Study 3 Part A showed that the SHARE-FI displayed adequate convergent and discriminant validity in this cohort (26). Consolidation of these results could indicate that, of the six instruments compared, the SHARE-FI is most suitable for use in adults living with heart failure, but these results need to be confirmed in a larger cohort.

Limitations

This study has some limitations; therefore, these results should be interpreted with caution. Firstly, this a single centre analysis with a limited sample. Consequently, rehospitalisation and mortality were unable to be analysed separately, instead a composite endpoint was chosen. All frailty instruments, except the Deficit Accumulation Index, are usually expressed as frail, pre-frail, and non-frail (or robust). For this analysis, due to the small cohort, the statistical power was too low to detect differences between three frailty categories; therefore, the pre-frail and non-frail groups were collapsed, and a dichotomous outcome of either frail or non-frail was reported. Using the three frailty categories may have allowed the discrimination between the frailty groups to be shown more effectively.

Secondly, the Deficit Accumulation Index is also not designed to be a dichotomous variable, rather a continuous ratio of deficits. As stated, for analysis, the cut-point of >0.25 was used to classify the participants as frail. This resulted in 81% of the cohort being classified frail according to the Deficit Accumulation Index, which the author acknowledges could be a ceiling effect. The cut-point used may have been too low, or some of the included deficits may not have been suitable for this cohort.

Thirdly, this study was undertaken in a heart transplant setting. Consequently, it was a younger cohort, primarily male and the majority experiencing NYHA class II and III

symptoms. Unfortunately, people who could not write or speak English or those with diagnosed dementia were also unable to be included, which is a significant limitation.

Despite the smaller numbers, these results suggest that the six frailty instruments compared in this study are suitable for heart failure research or risk-stratification. However, the clinical applicability of these instruments as part of frailty treatment plan is undetermined.

Implications for practice

This study was designed to help fill the knowledge gap surrounding frailty assessment in adults living with heart failure by highlighting the differences in predictive performance in a head-to-head comparison of multiple frailty instruments. While the results did not reach statistical significance, all frailty instrument models displayed satisfactory discrimination, and all but one instrument (the FRAIL scale) was able to predict the composite endpoint. As yet, frailty instruments' predictive ability has been a significant focus of the research regarding frailty in people with heart failure. However, it is anticipated that the focus will soon shift to the treatment of frailty, such as targeting frailty in pre-surgical patients through “prehabilitation” programs (44) and the potential for reversibility of frailty in select cohorts of people with heart failure. In younger people with heart failure, it is likely that frailty is caused by chronic disease processes, as opposed to being a process of ageing (5). Jha et al. (2017) demonstrated that frailty was reversible in a small number of patients’ post-heart transplantation, providing evidence their frailty was caused or driven by heart failure processes, as opposed to ageing (45). This can also be demonstrated by the high prevalence of frailty in this cohort, despite the younger age. With reversibility of frailty possible post-heart transplantation, there is scope to explore if other interventions to improve frailty are also effective in heart failure. The design of a frailty treatment plan would most likely involve periodic frailty assessments, so a frailty instrument that is sensitive enough to capture changes or improvements in frailty status over time would be essential.

5.13 Summary – Part B

Frailty was associated with increased odds of rehospitalisation and/or mortality. The physical and multidomain instruments performed comparably. All six frailty instrument models showed satisfactory discrimination. However, further investigation is required to

confirm the psychometric properties of these instruments for routine clinical use and as part of a frailty treatment plan in a larger more diverse heart failure cohort.

5.14 Conclusion

This chapter presented the results of a two-part study that evaluated the validity of frailty instruments potentially relevant for use in people living with heart failure. The first part involved comparing the convergent and discriminant validity of three physical frailty instruments, which revealed that the SVF and SHARE-FI displayed stronger validity than the Frailty Phenotype. Part A also provided clinically meaningful results regarding the suitability of the different frailty domains assessed by each instrument which showed that using an item regarding self-reported 'appetite' instead of 'weight loss' is appropriate in this population. However, using a self-reported item regarding 'ability to walk 100 metres' instead of an objective '5-metre walk speed test' produced highly varied results, suggesting this may not be appropriate. Part B was the logical next step which provided information on the validity of physical and multi-domain frailty instruments in a comparison of the predictive performance of six frailty instruments. This comparison revealed that the physical and multi-domain instruments performed comparably, with the 'physical' SHARE-FI and 'multi-domain' Deficit Accumulation Index associated with the highest odds for composite rehospitalisation and mortality. All adjusted frailty instrument models displayed adequate discrimination, but these results need to be confirmed in a larger cohort. While the results of Study 3 provide clinically meaningful information regarding the suitability of different frailty instruments in the context of heart failure, they also highlight that there is still work to do in defining the optimal means of frailty assessment in adults living with heart failure. The final chapter of this thesis will present the data integration and will discuss the future directions for research and the clinical recommendations of the FRAME-HF project.

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Chapter 6: Data integration, future directions, and conclusion

6.1 Preamble

The mixed methods FRAME-HF project, comprising three discrete, yet interrelated studies, was designed to help better understand frailty assessment in patients with heart failure. The findings of each of these studies have been presented in the preceding chapters and are summarised here.

Chapter 1 set the context for the FRAME-HF project by describing the clinical significance and implications of frailty in adults living with heart failure. Chapter 2 presented the systematic review (Study 1), which showed that the Frailty Phenotype (1) was the most commonly used instrument, and physical function was the most frequently assessed domain. The methods and ethical considerations of the FRAME-HF project are described in Chapter 3. Chapter 4 presented the results of Study 2a, a cross-sectional analysis that confirmed the poor correlation and inter-rater agreement between subjective clinician estimates of frailty versus a formal frailty assessment. Having established that subjective clinician estimates were an unreliable method of assessing frailty in a heart failure population, determining which instrument ought to be used for a formal frailty assessment was an important priority. Chapter 5 presented the outcomes of the two-part prospective cohort study (Study 3), which involved evaluating the validity of frailty instruments potentially relevant for use in adults with heart failure. Part A revealed that the SHARE-FI (2) and the St Vincent's frailty instrument displayed stronger discriminant and convergent validity than the Frailty Phenotype (1), suggesting they may be more suitable for a heart failure population. Part B compared the performance of six frailty instruments, which revealed that the SHARE-FI and the Deficit Accumulation Index had the highest odds for composite rehospitalisation and mortality at 12 months, though this was non-significant. All six instrument models performed similarly, suggesting all are suitable for risk stratification and/or research purposes; their applicability for routine clinical practice is yet to be determined.

This final chapter addresses the four research questions underpinning the FRAME-HF project presented initially in Chapter 1. The individual FRAME-HF studies addressed the first three research questions. The results of each study were reported in stages as the data

were analysed and published and/or disseminated separately. The FRAME-HF project findings were then synthesised and integrated to answer the final research question - "What is the most suitable and clinically relevant frailty instrument/(s) for use in adults living with heart failure?" Finally, the key clinical recommendations arising from this project for implementation and future research will be described to conclude.

The FRAME-HF project research questions:

6.2 Research Question One: How is frailty measured in adults with heart failure, and which frailty domain is most frequently assessed?

The FRAME-HF systematic review (Study 1, presented in Chapter 2) identified seven unique frailty instruments from 20 studies that assessed frailty in a heart failure population. The most widely used instrument was the Frailty Phenotype, used in 55% (n=11) of studies. However, the majority of studies (n= 8) (3-10) used a modified version of the original Frailty Phenotype instrument. Of the seven frailty instruments identified, none have been validated for use in patients with heart failure (11). Furthermore, there is also a lack of global consensus regarding which frailty assessment instrument or method is most suitable for a heart failure population (11-13).

The most frequently assessed domain across the instruments was physical function, with all seven frailty instruments containing an item that assessed physical function (14). This focus on physical frailty domains in the context of heart failure is somewhat perplexing, as those with heart failure often experience associated physical limitations (15), which could affect their ability to undertake physical tests and result in potential misclassification of frailty (12, 16). Whilst many of the seven instruments identified in Study 1 assessed similar domains (11). There are some distinct differences across the instruments, such as some containing an objective handgrip strength measurement requiring the use of specialised equipment (i.e., dynamometer) or five-metre walk speed test, which denotes that a clinician is present to undertake the test. These distinct differences affect the rates of frailty between instruments and their applicability in patients with heart failure.

Most studies identified in Study 1 assessed frailty in community-dwelling individuals or outpatients with heart failure rather than inpatients. Consequently, there is insufficient data for comparison, and there is no consensus about which time-point is most appropriate for a

frailty assessment to occur. As heart failure has been reported to be the most common cause of hospitalisation in older adults (17, 18), there is an opportunity for frailty assessment to be routinely undertaken while these individuals are hospitalised. However, the uncertainty regarding the most appropriate time for frailty assessment does raise questions regarding the potential fluctuation of frailty over time, e.g., whether an individual's frailty status changes when they are acutely unwell and hospitalised, as opposed to post-discharge or post-recovery; and the functionality of the assessment, i.e., what will be done with frailty assessment data once collected.

To the author's knowledge, Study 1 was the first systematic review to focus on the assessment instruments and the specific frailty domains assessed in the context of heart failure. However, there have been several other review articles that address frailty in a heart failure population (13, 19-22), with the following similar themes identified: frailty is increasingly being assessed in patients with heart failure, but there is no agreement of which assessment approach is best (13); frailty assessment is highly predictive of worse outcomes, such as, rehospitalisation and mortality, but can vary depending on what instrument was used to assess frailty (19, 21); and that prevalence rates between instruments is highly variable (20, 22). These results strengthen the FRAME-HF systematic review findings and further highlight the need for a more unified frailty assessment approach for adults with heart failure. The current ambiguity and lack of guidance regarding frailty assessment in this population could impact treatment decisions and contribute to worsening emotional and physical health if frailty is not reliably identified, underscoring the need for further investigation into the 'optimal' way to assess for frailty in adults living with heart failure.

6.3 Research Question Two: How reliable are clinician estimates of frailty compared to a formal frailty assessment in determining the frailty status of adults living with heart failure?

Study 2 (presented in Chapter 4) revealed that clinician estimates of frailty were poorly correlated to the formal frailty assessments and that the inter-rater agreement was only fair (1, 6). These results confirm that subjective clinician estimates are not a reliable method of determining the frailty status of adults living with heart failure. Of the three groups of

cardiovascular clinicians who provided estimates, the allied health frailty estimates showed the strongest correlation and agreement to the formal frailty assessment, though this was only moderate. Even when stratified by patient characteristics previously associated with frailty, such as NHYA class III-IV (6) and participant gender (23), clinicians still poorly identified frailty. Estimates of frailty have been evaluated against formal assessment in other health populations, i.e., acute cardiology patients (24), community-dwelling older persons (25), and individuals undergoing haemodialysis (26) and similar unfavourable results have been demonstrated (24-26). This provides further confirmation that subjective estimates of frailty are an unreliable method of assessing frailty across multiple health populations and should not replace formal frailty assessment in the clinical setting.

The absence of a universally accepted definition of frailty and consensus regarding the 'optimal' frailty instrument for use in adults living with heart failure in part may explain why subjective estimates of frailty, such as the 'end-of-the-bed' or 'eyeball' test continue to be applied in clinical practice (16, 27). Study 2 demonstrated that frailty misclassification by the clinicians was common, which could lead to adverse health consequences and potential legal repercussions if surgical or other advanced treatments are delayed or conversely if inappropriate advancement of treatment occurs based on incorrect frailty status (28).

The results of Study 2 confirm the importance of assessing frailty using a formal instrument and can help justify the importance of integrating routine formal frailty assessment, using a valid instrument, not subjective estimates, into the clinical management of adults living with heart failure. Therefore, as was identified in the FRAME-HF systematic review and with subjective estimates now established as unreliable, the validation of a suitable and clinically relevant instrument/(s) for use in adults living with heart failure was a high priority focus of the final study of this doctoral project.

6.4 Research Question Three: What are the validity of frailty instruments potentially relevant for use in adults living with heart failure (Study 3)?

Study 3 (presented in Chapter 5) was designed to evaluate the validity of six physical frailty instruments (three physical and three multi-domain). Because the Frailty Phenotype (1) - and various modified versions - are the most commonly used frailty instruments, the Frailty Phenotype and two modified versions, the SHARE-FI (2) and SVF (6, 14), were chosen for

Study 3 Part A, which evaluated their convergent and discriminant validity in a cohort of adults living with heart failure. The SVF had the highest correlation to the sub-constructs; and the SHARE-FI displayed the greatest ability to discriminate between normal and abnormal scores of the sub-construct assessments, demonstrating that the SVF and SHARE-FI had stronger validity in a heart failure cohort and may be more suitable than the original Frailty Phenotype (14). This finding is important as it raises concern regarding the suitability of the most frequently used frailty instrument in heart failure studies to date (11).

Another key finding was that despite all three instruments being versions of the Frailty Phenotype, the frailty classifications and the proportion of those positive across the five frailty domains were highly variable (14), emphasising that even conceptually similar instruments can provide different results. While information regarding the suitability of different frailty instruments in heart failure is widely available (10, 16, 29, 30), information regarding the suitability of the individual frailty domains for a heart failure cohort is not. The domain of particular interest to heart failure researchers and clinicians is 'unintentional weight loss', which is difficult to assess due to the fluid retention and frequent weight fluctuations often experienced by those with heart failure (15, 16). The results from Study 3 Part A found that substituting the 'unintentional weight loss' domain with a 'diminished appetite' domain was appropriate, with consistent results for this domain demonstrated across the three instruments. In contrast, the 'slowness' domain was the least consistent, demonstrating that replacing the 'five-metre walk speed test' with a self-reported domain of 'difficultly walking 100 metres' may not be appropriate (14). These findings highlight the importance of careful deliberation before modifying frailty instruments and that further investigation of the most appropriate frailty domains for use in adults living with heart failure is still required.

Study 3 Part B compared the performance of six frailty instruments' ability to predict composite rehospitalisation and mortality at 12 months post initial frailty assessment in adults living with heart failure. This study found that all six instruments performed similarly, with no single instrument established as the 'optimal' frailty instrument for use in adults living with heart failure. Each instrument, except the FRAIL scale, associated frailty with an increased odds of composite rehospitalisation and mortality, and all six adjusted frailty instrument models displayed acceptable discrimination when classifying the study

outcomes. The SHARE-FI, a physical frailty instrument, and the Deficit Accumulation Index, a multi-domain frailty instrument, displayed the greatest discrimination between the 'frail' and 'non-frail' groups, suggesting that both physical and multidomain instruments are suitable for risk-stratification and research purposes in adults with living with heart failure.

Our results differed from a recent study which demonstrated that a multi-domain instrument, such as the Deficit Accumulation Index, had superior predictive ability than a physical instrument (30). Yet, our results were comparable to another study where a physical and multi-domain instrument performed similarly (10). The frailty classification across the six instruments was also highly variable (33-81%), consistent with the literature that has found wide variation in the frailty classification applied to the heart failure population (11, 13, 16, 22). This inconsistency between frailty instruments creates challenges for clinicians and researchers alike by adding to the uncertainty surrounding the 'optimal' way to measure frailty in the context of heart failure. Furthermore, it impedes the widespread uptake of routine frailty assessment in clinical practice, triggers concern over the reported prevalence rates of frailty due to the potential floor and ceiling effects, and makes the comparison of outcomes between studies difficult.

Unfortunately, the results of Study 3 were unable to recommend a single frailty instrument as the 'optimal' frailty instrument for use in adults living with heart failure. To generate new knowledge and insights, the FRAME-HF project data were integrated to answer the project's final research question, which aims to determine the most suitable and clinically relevant instrument/(s) for use in this population, as described below.

6.5 Research Question Four: What is the most suitable and clinically relevant frailty assessment instrument/(s) for adults with heart failure?

The FRAME-HF results confirmed that subjective clinician estimates of frailty were an unreliable method of assessing frailty in adults living with heart failure and also provided information regarding the validity of all six frailty instruments in this cohort. Based on these results alone, there was insufficient evidence required to conclusively recommend an individual instrument as the 'optimal' frailty instrument for use in this population. However, when the FRAME-HF findings were integrated (Refer Table 6.1), it revealed that, of the six

instruments compared, the SHARE-FI (2) might be the most suitable and clinically relevant instrument for a heart failure population.

While the Frailty Phenotype was identified as the most widely used in the FRAME-HF systematic review (11), the SHARE-FI is becoming more widely applied in this population. The SHARE-FI has been used in five different heart failure studies on a combined total of 1447 patients with heart failure (inpatients n= 1402 and outpatients n= 45), with frailty prevalence between 50-86% (8, 9, 14, 31, 32). As described in Chapter 3, the SHARE-FI was designed as a practical alternative to the Frailty Phenotype for the primary care setting and was created using the same five domains as the Frailty Phenotype (2). However, it substitutes the 'weight loss' domain with a 'diminished appetite' domain and the five-metre walk test with 'ability to walk 100 metres', which could be more suitable for a heart failure population. In Study 3, the SHARE-FI displayed better overall convergent and discriminant validity than the Frailty Phenotype and demonstrated the strongest predictive ability and discrimination, making it most consistent of the six instruments compared in the FRAME-HF project. The meta-inferences outlined in Table 6.1 from the integration of these findings suggest that the SHARE-FI may be the most suitable and clinically relevant for use in adults living with heart failure.

The utility of the SHARE-FI in a heart failure population is yet to be determined. However, the doctoral researcher's experience was that the SHARE-FI was easy to use in a heart failure cohort; and would likely be straightforwardly adapted to the heart failure clinical setting. The SHARE-FI also has free online calculators available and does not require extensive training or equipment, making it quick for clinicians to use and simplifying data collection in the clinical setting. For these reasons, the suitability and validity of the SHARE-FI for routine clinical care should be a focus for further psychometric evaluation in a larger heart failure cohort.

In contrast, with the growing focus on multi-domain assessment in the context of heart failure (12, 16, 30, 33, 34), further psychometric evaluation of multi-domain instruments in a larger heart failure cohort is also required. As demonstrated in Study 3, the multi-domain Deficit Accumulation Index (35) displayed comparable predictive performance to the SHARE-FI, indicating its suitability for risk stratification and potential applicability for routine clinical care in adults living with heart failure. One of the advantages of the Deficit Accumulation

Index is that it can be derived from routinely collected data or hospital database and can be automatically calculated for each patient, eliminating the need for a specially trained or accredited clinician to undertake an assessment. With the recent focus on 'big data' or large linked datasets in clinical research, this concept may soon be more feasible. A recent study of patients with heart failure (n= 8893) (36) demonstrated that an automatically derived modified Deficit Accumulation Index (37) of deficits identified from relevant International Classification of Diseases codes adequately predicted short term mortality (36). However, if automatically derived frailty scores are used in the clinical setting, there must be comprehensive strategies to translate the score into something clinically meaningful capable of informing a frailty management plan, rather than merely a routinely collected but seldom acted upon risk-stratification score.

When considering the utility of a Deficit Accumulation Index, particularly one that is automatically derived, it should be noted that there are still gaps in knowledge regarding how frailty instruments perform over time. Specifically, how sensitive would the various frailty instruments be to detect changes in frailty status overtime when repeated measures are required? Would an automatically derived Deficit Accumulation Index be sensitive enough to detect subtle changes in frailty status over time, or would a physical frailty instrument more suitable? These questions will be answered in a future research study.

A recent position paper from the Heart Failure Association of the European Society of Cardiology (16) proposes that a new frailty definition should be used for heart failure. They suggest frailty in patients with heart failure is: "a multidimensional dynamic state, independent of age, that makes the individual with heart failure more vulnerable to the effect of stressors" (16) (p. 1303). The Heart Failure Association of the European Society of Cardiology also proposes that a new instrument should be developed for the heart failure context that encompasses four main domains: clinical, physical-functional, cognitive-psychological, and social (Refer Figure 6-1). The low mean age of the FRAME-HF cohort and the moderate to high prevalence of frailty across the instruments (14) supports this definition and confirms that frailty in adults living with heart failure is likely independent of age. This proposed new instrument takes a multi-domain view of frailty, which, as mentioned, may be more appropriate for heart failure (11, 12, 33). And as demonstrated in Study 3, multi-domain frailty instruments are equally as suitable for risk-stratification in

patients with heart failure as physical frailty instruments, therefore, further investigation of their clinical applicability in adults living with heart failure should also be explored.

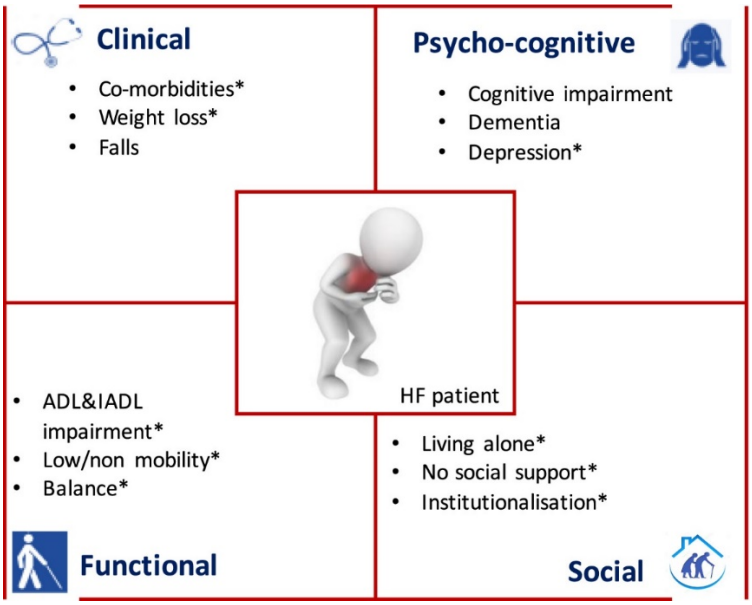

Figure 6-1 The Heart Failure Association (HFA) Frailty Score.

Key: Reversible and/or treatable variables are identified by asterisks. ADL, activities of daily living; IADL, instrumental activities of daily living. Image from Vitale et al. (16) (p. 1300), with permission from Elsevier (License no. 4962931480500, Dec 06, 2020).

While the results of FRAME-HF demonstrate that the SHARE-FI (2) may be the most suitable and clinically relevant for use in adults with heart failure, they are unable to irrefutably confirm which instrument is the 'optimal' frailty instrument, only recommend an instrument for further psychometric evaluation. The FRAME-HF project does, however, provide important novel information for heart failure clinicians wishing to undertake frailty assessment but also signals there is still much work to do, as will be discussed in the following section.

Table 6-1 Joint display of findings.

Research Question Five: What is the most suitable/clinically relevant frailty instrument/s for use in adults with heart failure				
Study 1: A systematic review exploring how frailty is assessed in heart failure	**Study 2 Cross-sectional analysis of clinician estimates of frailty compared to formal frailty assessment in adults with heart failure**	**Study 3- Part A: Baseline analysis evaluating the validity of three physical frailty instruments in adults with heart failure**	**Study 3 - Part B: 12-month outcome analysis comparing the predictive performance of six frailty instruments in adults with heart failure**	**Meta-inferences**
• Seven unique frailty instruments were identified from 20 studies that assessed frailty in heart failure patients	• Clinicians overestimated the 'non-frail' group by more than twofold and underestimated those who were 'pre-frail' and 'frail'	• The SVF instrument displayed the highest correlation to the sub-constructs (NHYA classes, AKPS scores and EQ5D-5L dimensions, DMI-10 and MoCA score)	• The prevalence of frailty varied widely across the six different instruments (33- 81%)	1. The SHARE-FI displayed the most consistent results of the three physical frailty instruments, i.e., low to moderate correlation to the sub-constructs assessed (convergent validity) and the strongest discrimination between normal and abnormal scores of the sub-constructs and between inpatients and outpatients assessed as 'frail' (discriminant validity)
• The Frailty phenotype (a physical frailty instrument) is the most frequently used frailty instrument in heart failure (the majority of	• Frailty was misclassified in both inpatients and outpatients and males and females	• The SHARE-FI also displayed low to moderate correlation to the sub-constructs	• The multi-domain instruments reported a higher prevalence of frailty	

studies use a modified version)				2. The best time to assess frailty needs to be defined, i.e., is it better to assess for frailty while a patient is hospitalised or post-discharge and/or post-recovery? At what point in the heart failure illness trajectory is the most appropriate time to assess frailty?
• The Comprehensive Geriatric Assessment and Deficit Accumulation Index, (both multi-domain instruments) have only modest use in heart failure research	• When stratified by NYHA class III-IV (severe heart failure symptoms at rest) 21% were estimated as 'frail' compared to 45% formally assessed as 'frail'	• The SHARE-FI and SVF detected the most statistically significant group differences between normal and abnormal scores of the sub-constructs within the three frailty categories (frail, pre-frail and non-frail)	• Sixty-three per cent of participants had either died or been rehospitalised within the 12 months follow-up period	
• All seven frailty instruments assessed physical function/mobility, making this the most frequently assessed domain	• Correlation and inter-agreement between pooled clinician-estimated frailty and formally assessed frailty was fair	• Both the FP and SHARE-FI were able to discriminate between inpatients and outpatients who were classified as 'frail'	• All instruments (except the FRAIL scale) were associated with increased odds of rehospitalisation and/or mortality	3. A validated instrument for heart failure is urgently needed, one that is quick and easy to use in a resource-restricted clinical environment
• The majority of studies assessed frailty in community dwellers/outpatients	• Correlation and inter-rater agreement between allied health-estimated frailty and	• The prevalence of frailty between the instruments and the percentage of patients classified as	• The Deficit Accumulation Index and the SHARE-FI had the highest odds for	4. There is a need to implement routine formal frailty assessment in patients with heart failure

	formally assessed frailty was moderate	positive in the five frailty domains according to each instrument was highly variable	rehospitalisation and/or mortality	5. Multi-domain and physical frailty instruments are both suitable for assessing frailty for research and risk stratification purposes but their applicability as part of frailty management plan where repeated frailty assessments may be required over time is still to be determined 6. The SHARE-FI displayed convergent and discriminant validity, adequate predictive ability, and strong discrimination between participants who were 'frail' and 'non-frail', suggesting that the SHARE-FI may be the most suitable/clinically relevant instrument for heart failure
• There are no frailty instruments that have undergone large scale validation in a heart failure population	• Subjective clinician estimates of frailty did not show strong correlation or agreement to formal frailty assessment	• Replacing 'unintentional weight loss' with 'diminished appetite' produced similar results across the three instruments but replacing the five-metre walk speed test with 'ability to walk 100 metres' produced inconsistent results	• All instrument models displayed adequate discrimination (i.e., good sensitivity and satisfactory C-statistic values)	
• There is no consensus regarding which assessment approach/instrument is the most suitable for heart failure (i.e. physical frailty instrument or multi-	• Subjective estimation of frailty is not a suitable replacement for formally assessed frailty	• The SHARE-FI and SVF displayed stronger convergent and discriminant validity than the frailty phenotype	• The SHARE-FI and Deficit Accumulation Index had the highest C-statistic value of 0.73	

domain instrument) or when is the most appropriate time to assess frailty (i.e. in community/clinic or hospital)				
			• The multi-domain and physical frailty instruments performed similarly	

Key: FP, Frailty Phenotype; SHARE-FI, Survey of Health, Ageing and Retirement in Europe Frailty Instrument; SVF, St Vincent's Frailty Instrument; SVF +, St Vincent's Frailty Instrument plus cognitive and mood domains; FRAIL scale, Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight scale; and DAI, Deficit Accumulation Index.

6.6 Future directions

Frailty is primarily considered a 'geriatric syndrome' due to its association with age-related biological changes and its higher prevalence in older adults (38). While this is true, the FRAME-HF project has demonstrated that frailty is not necessarily age-related and is often experienced by younger 'middle-aged' people living with heart failure, particularly those experiencing the advanced stages of heart failure (14). Similar results in two recent heart failure studies found that a quarter (39) to a third (6) of younger patients (mean age of 59 ± 2 and 53 ± 12 years) were frail on referral for heart transplantation or implantation of a ventricular assist device (6, 39). The presence of frailty in younger individuals with advanced heart failure challenges the assumption that frailty predominately occurs due to age-related changes. This phenomenon highlights the importance of understanding the origin of frailty in younger heart failure populations as it may be related to their advanced disease processes, i.e., 'disease-related frailty as opposed to 'age-related frailty', effectively making them 'biologically aged' rather than 'chronologically aged' (12, 13).

Nonetheless, despite the FRAME-HF project having a typically lower mean age than other heart failure studies (8, 40), evidence shows that the majority of people with heart failure are older adults, with prevalence increasing significantly with age (41). Similarly, the prevalence of frailty increases markedly with age (38, 42). As a result, most adults living with heart failure and experiencing frailty will likely be older persons with associated complex care requirements. When planning care for older persons with heart failure and frailty, a multidisciplinary team (MDT) approach should be considered, one that involves both the cardiology/heart failure and geriatric teams and specialised advanced practice nurses allied health professionals (43).

The use of a MDT approach is considered the 'gold standard' model of care for people with heart failure to reduce recurrent rehospitalisation and can include self-care education, telemonitoring, structured telephone support, clinical reviews, pharmacological management, and cardiac rehabilitation/exercise interventions (44). The use of a MDT approach in conjunction with a comprehensive geriatric assessment has also been suggested as the 'gold standard' of care for frail older adults (45). As described in Chapter 2, the comprehensive geriatric assessment (CGA) is a form of structured geriatric assessment commonly performed by geriatricians. The CGA can be used to identify frailty but has had

only modest use in the heart failure population, likely due to its time-consuming nature and the specialist training required to undertake this form of assessment (11). The recently published consensus guidelines from the International Conference for Frailty and Sarcopenia regarding 'Screening for and managing the person with frailty in primary care' recommend a coordinated, integrated MDT approach, involving primary care clinicians, geriatricians, allied health professionals, caregivers and patients, as the ideal standard of care for frail older adults (46). These guidelines also recommend that brief frailty screening should be undertaken (as opposed to a more wide-ranging frailty assessment requiring various objective measures) in the primary care setting in the first instance, using a short instrument such as the FRAIL scale (47). If a patient is identified as 'frail' or 'at-risk of frailty', they should be referred to the geriatric team for a comprehensive geriatric assessment and management of their complex care needs using an integrative MDT approach (46). Brief frailty screening would likely be suitable for older heart failure patients in the primary care setting, i.e., in the outpatient heart failure clinic or the home as part of community heart failure care; or when patients are admitted to the ward using the FRAIL scale or an automatically derived Deficit Accumulation Index (35).

Currently, there are limited evidence-based interventions available to prevent or improve frailty in adults living with heart failure. However, various evidence-based frailty interventions and management strategies are available targeting older adults (46, 48-50). A recent meta-analysis of older adults (n= 4794) found that interventions using primarily resistance-based exercise and nutrition supplementation improved frailty more than the control (48). Another meta-analysis of community-dwelling older adults (n= 655) found that physical exercise interventions helped improve cognition and mental flexibility in those with frailty syndrome (50). Education and training have also been highlighted as an essential strategy to help improve frailty screening and management. Yet, a recent systematic review identified no studies that addressed educational strategies for frailty (51), so this is another important focus for future research.

Managing the effects of frailty before surgical intervention is also an essential priority for adults with heart failure, especially those undergoing heart transplantation, mechanical assist device insertion, or minimally invasive valve implant or replacement procedures. The role of 'pre-habilitation', i.e., 'the practice of enhancing an individual's functional capacity to

enable them to withstand major surgery' (52) (p. 401); with a focus on pre-operative physical rehabilitation and nutritional support, needs to be explored further as it could be a potentially beneficial solution for patients undergoing various surgical procedures, including heart and lung transplantation (53). Pre-operative physical and nutritional support may enhance recovery and reduce mortality (54, 55). Studies that include interventions such as, exercise programs/physical training, cognitive training, nutritional support are effective at improving frailty in older adults (56-59) and prescribing physical activity with a resistance training component, involving exercises to target muscle wastage and mobility loss, have also been shown to reduce fatigue, lower the rate of disability, and decrease the likelihood of admission to hospital (56, 60, 61). The effectiveness and applicability of these strategies in adults living with heart failure is yet to be evaluated in a large clinical trial. The application of a physical exercise program for those with heart failure would need to be carefully tailored to suit people with poor exercise tolerance; it may be expedient to ensure that heart failure symptoms are as adequately managed as possible before the commencement of any exercise program, although, the unpredictable nature of heart failure symptoms may make this difficult (53).

The recently published 'Asia-Pacific Clinical Practice Guidelines for the Management of Frailty' provide a list of suggested recommendations for improving and treating frailty (in older adults) (60) as outlined below.

Strong Recommendations:

1. We strongly recommend that frailty be identified using a validated measurement tool.
2. We strongly recommend that older adults with frailty be referred to a progressive, individualized physical activity program that contains a resistance training component.
3. We strongly recommend that polypharmacy be addressed by reducing or de-prescribing any inappropriate/superfluous medications.

Conditional Recommendations:

4. We conditionally recommend that persons with frailty are screened for causes of fatigue.
5. We conditionally recommend that older adults with frailty who exhibit unintentional weight loss should be screened for reversible causes and considered for food fortification/protein and caloric supplementation.

6. We conditionally recommend that vitamin D be prescribed for persons found to be deficient in Vitamin D.

No Recommendation:

7. We have no recommendation for the provision of an individualised support and education plan for older adults with frailty (60) (p. 566).

The first recommendation highlights the importance of using a validated measurement instrument when identifying frailty. As mentioned previously, the FRAME-HF systematic review revealed that (11), a validated instrument for heart failure, is currently lacking. Therefore, the validation of a frailty instrument for use in adults living with heart failure (or development of a new heart failure frailty instrument) is an important priority for future research. The second strong recommendation is that older adults be referred for an exercise program with a resistance training component. The implementation of a tailored exercise program for heart failure patients as part of a pre-habiliation program is yet to be featured in the literature, making it another crucial area for future research. Reducing polypharmacy is also an important consideration for people living with heart failure, as the prescription of numerous potentially inappropriate or superfluous medications is also common in this population (62).

There is potential to examine the efficacy of the above interventions in adults living with heart failure and/or propose novel interventions. Strategies to achieve this in an Australian heart failure context could involve: increasing frailty focus within the next National Heart Foundation (NHFA)/ Cardiac Society of Australian and New Zealand (CSANZ) 'Guidelines for the Detection and Management of Heart Failure" (41); or exploring possibilities for a separate NHFA/CSANZ consensus statement with specific guidelines and suggested recommendations for frailty management in adults living with heart failure, taking into consideration the distinct groups of heart failure patients that can experience frailty (i.e., older adults and younger/middle-aged people whom likely develop frailty as a result of their chronic disease processes). Although, as MDT collaboration is considered the 'gold standard' of care for people living with frailty (45) and heart failure (44), perhaps a larger panel of experts should be consulted, e.g., members of the Australian and New Zealand Society for Sarcopenia and Frailty Research or the Australian Association of Gerontology. Asking other expert groups to contribute would provide a key collaborative opportunity and may

subsequently help improve the integration of heart failure and frailty services in the clinical setting.

6.7 Recommendations from this thesis

At the conclusion of the FRAME-HF project, there are four main clinical recommendations suggested for implementation and future research.

6.7.1 Recommendation 1: Assess frailty using a formal instrument

Clinicians should undertake routine frailty assessment in patients diagnosed with heart failure, using a formal frailty assessment instrument. The continued use of subjective frailty estimates, such as the '*end-of-the-bed*' test is strongly discouraged.

6.7.2 Recommendation 2: A validated frailty instrument for heart failure is urgently needed

An instrument that is explicitly validated for use in adults living with heart failure is still required, one that is quick and easy to administer in a resource-restricted clinical environment. The SHARE-FI shows potential as an 'optimal' instrument for use in adults living with heart failure and further psychometric investigation of this instrument could be a valuable theme for future research.

6.7.3 Recommendation 3: Optimal timing of frailty assessment in heart failure must be defined

Further research regarding the most appropriate time to assess frailty in the clinical setting needs to be evaluated, i.e., is inpatient or outpatient frailty assessment preferable and at what time-point in the heart failure illness trajectory should frailty be assessed? Evaluating potential changes in frailty status over time and at different stages of the illness trajectory should be a high priority for future research.

6.7.4 Recommendation 4: An integrated multidisciplinary approach to frailty management should be implemented

Further investigation regarding heart failure-specific interventions to manage and/or improve frailty (i.e., 'pre-habilitation' or resistance training programs) is required. Increasing frailty focus in heart failure programs and integration of cardiology and/or heart failure and geriatric teams using a MDT model of care should be prioritised. For older adults with heart failure,

the inclusion of a member of the geriatric team in the heart failure clinical ward round and/or the introduction of specialised advanced practice frailty nurses to the MDT could be advantageous and presents a key area for future research.

6.8 Strengths and limitations

The FRAME-HF project has many strengths, such as its mixed methods design, which helped produce the practical and clinical meaningful findings. FRAME-HF also presents the largest number of frailty instruments compared in adults with heart failure to date, evaluating the validity and predictive performance of the different instruments and adds important novel information regarding how best to assess frailty in adults living with heart failure.

There are also some limitations which should be noted. Firstly, this project comprises non-randomised single-centre analyses with limited sample sizes. Larger participant sample sizes were planned, but the confines of a resource-restricted team, a lack of funding, and a doctoral program's time restrictions resulted in a significantly smaller sample than anticipated and most likely affected the generalisability of the project's findings.

This doctoral project also focuses on a specific group of patients, i.e., adults living with heart failure; however, there was a significant number of participants who were also awaiting heart transplantation. The participants awaiting heart transplantation were included as they met the project inclusion criteria, but a heart transplant context was not the focus of this doctoral project; rather, a 'general' heart failure population. The inclusion of participants awaiting heart transplantation resulted in a younger cohort than expected in a 'general' heart failure population, which may have inadvertently affected our results' clinical applicability to the broader heart failure population.

Participants who were unable to speak or write in English and people with diagnosed dementia or other cognitive illness that prevented informed consent were also excluded from this project, which is another significant limitation. Unfortunately, the lack of resources and availability of an appropriate interpreter service to undertake informed consent or translate the case report forms and the limitations of a doctoral program did not allow time to explore alternative informed consent procedures. Proxy consent was considered, but as a large proportion of the case report forms were reliant on patient-reported variables, this was not a feasible alternative. The doctoral researcher fully

acknowledges the inequities of excluding people with dementia in clinical trials and accepts that this project, regrettably, contributes to this misrepresentation. Developing strategies to improve the representation of people living with dementia in frailty and heart failure clinical trials is crucial for future research.

Finally, while the FRAME-HF project did not provide enough robust psychometric evaluation to validate a frailty instrument/(s) for use in adults living with heart failure, it provides a powerful platform and foundation for the focus of the author's post-doctoral work.

6.9 Conclusions

The FRAME-HF project has provided important novel information regarding the assessment of frailty in adults living with heart failure, namely: it revealed how frailty was being assessed in heart failure studies; identified the shortage of validated frailty instruments for use in a heart failure population; justified the necessity of routine formal frailty assessment (not subjective estimates of frailty); evaluated he validity of three physical instruments which revealed that the most commonly used instrument in people with heart failure might not be the ideal choice for this population; and lastly compared the predictive performance of six frailty instruments, which revealed that multi-domain and physical frailty instruments were comparable, suggesting that both are suitable for risk-stratification and research purposes. The applicability of the instruments evaluated in this project for routine clinical care and as part of a frailty management plan is undetermined and will be a focus of the doctoral researcher's future work. Integration of the results revealed that the SHARE-FI could be a potential 'optimal' instrument for heart failure. The psychometric evaluation of this instrument is a priority area for future research. International consensus on the global frailty definition and the 'optimal' assessment instrument for use in adults with heart failure must be reached, and a validated instrument for this population is urgently needed. Frailty assessment should be incorporated into the daily practice of cardiovascular clinicians and must be universally accepted as an essential part of the clinical management of adults living with heart failure.

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Appendicies

Appendix 1: Published manuscripts associated with this thesis

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Manuscript 1 and 2: Sage journal publications do not require permission for the author to reuse a published manuscript in their thesis/dissertation.

Manuscript 3: Springer published manuscript reused with permission from Springer Nature, License number 5032210714810, March 18, 2021.

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Frailty assessment instruments in heart failure: A systematic review

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Abstract

Background: Frailty is an independent predictor of mortality across many conditions. Reported rates of frailty in heart failure range from 15% to 74%. There are several instruments available to assess frailty; however, to date there has been no consensus on the most appropriate instrument for use in individuals with heart failure.

Aims: To identify how frailty is assessed in individuals with heart failure and to elucidate which domains of frailty are most frequently assessed.

Methods: Key electronic databases were searched (MEDLINE, COCHRANE Central and CINAHL) to identify studies that assessed frailty in individuals with heart failure using a formal frailty instrument.

Results: Twenty studies published in 24 articles were included, for which a total of seven unique frailty instruments were identified. The most commonly used instrument was the Frailty Phenotype (n= 11), with the majority of studies using a modified version of the Frailty Phenotype (n= 8). The second most commonly used instrument identified was the Comprehensive Geriatric Assessment (n= 4).

Conclusion: There is an increasing interest in the assessment of frailty, but, to date, there is no frailty instrument validated specifically in the heart failure population.

Keywords

Frailty, heart failure, assessment

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Introduction

Frailty is a multidimensional syndrome characterized by a state of increased vulnerability to acute stressors, such as hospitalization, falls and infection. It is an independent predictor of mortality[1,2] and is the most problematic expression of population ageing.[3] With growing focus on multimorbidity, this construct has increasing utility.[4] Frailty is most commonly defined as meeting three out of five phenotypic criteria: low physical activity, unintentional weight loss, slow walking speed, weak grip strength, and/or exhaustion.[5]

Heart failure is a common yet complex cardiac syndrome, developing as a result of structural or functional damage to the heart which reduces its ability to fill with and/or pump blood effectively.[6,7] The prevalence of heart failure increases significantly with age[8] and is associated with high morbidity and mortality.[9,10] Heart failure is a leading cause of hospitalization and general practitioner consultation, particularly in the elderly population.[10]

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Table 1. Search terms.

Database	Search terms
Medline	*Frailty:* MeSh – frail elderly, frailty as a key word, vulnerability, disability, cachexia, sarcopenia, hand grip, gait speed *Heart failure:* heart failure.mp., Ventricular dysfunction, left.sh. Cardiomyopathy.mp. Left ventricular ejection fraction.mp. *Measurement:* measurement as key word, instrument, outcome measure, outcome assessment, hand grip
Cochrane Central and CINAHL	*Frailty:* frail elderly, frailty as a key word, vulnerability, disability, cachexia, sarcopenia, hand grip, gait speed *Heart failure:* heart failure, ventricular dysfunction, cardiomyopathy, left ventricular ejection fraction

The high prevalence of frailty in heart failure is well documented[11–13] and as such it has been identified as an emergent area of research priority.[14] The reason for this is complex and multifaceted. Some of these considerations are determining prognosis and assisting in the assessment of therapies, particularly those that are invasive.[15] Frailty has been shown to predict adverse outcomes in heart failure.[12,16,17] However, the variability in defining frailty and the use of diverse measures have made it problematic to compare the prevalence of frailty and its impact on outcomes between studies.

Aims

The purpose of this review was to examine how frailty is assessed in individuals with heart failure.

The four key objectives of this review are:

(a) Summarize the available instruments that have been used for frailty measurement in heart failure;
(b) Highlight the core domains of frailty assessments;
(c) Identify the strengths and limitations of the instruments;
(d) Discuss implications for future heart failure clinical research and practice.

Methods

Following consultation with a health librarian, key electronic health related databases (MEDLINE and CINAHL and the COCHRANE Central) were searched from 2001 to 2016. In 2001, Fried published her seminal paper on the impact of frailty in cardiovascular disease;[5] accordingly it was selected as the start point for this review. Search terms included are listed in Table 1. Original studies were selected that included participants with a diagnosis of heart failure, that is, individuals exhibiting heart failure symptoms or receiving treatment for heart failure, and studies must have addressed measurement of frailty using a structured instrument. Only original studies were included; conference abstracts, reviews and editorials were excluded.

First, articles were extracted from the electronic database. Following this, they were screened against the eligibility criteria based on title/abstract. Articles then underwent full text review by two independent researchers (JM and LM); where necessary a third researcher (PJN) was consulted. In the case of multiple studies drawn from the same data set, the original paper was included in the summary table.

The review was conducted in accordance with the PRISMA guidelines.[18]

Quality assessment of included studies

Quality assessment of included studies was undertaken by two independent reviewers in accordance with the Joanna Briggs Institute (JBI) Critical Appraisal Checklists for case control studies, studies reporting prevalence data, cohort studies and randomized control studies outlined in the *JBI Reviewers' Manual*: 2014 edition (see Supplementary Material online, Tables 1–4).[19] To the authors' knowledge the included articles also conformed to the standards outlined in the Declaration of Helsinki.[20] Due to heterogeneity of frailty assessment among the included articles meta-analysis was not performed. Results are summarized in tabular and narrative form.

Results

The search strategy retrieved a total of 740 articles. Following the removal of duplicates, 699 were screened. From this, 664 were excluded based on inappropriate title/abstract with the remaining 35 undergoing full-text review. After consensus was gained, 24 articles were included in this review (Figure 1). Seven different frailty instruments were identified from the 24, and from these 20 were identified as original studies. The most commonly utilized frailty instruments (n=11 (55%)) were based on Frailty Phenotype (FP),[5] with the majority (n=8) using modified versions of the original tool[17,21–28] with one study assessing a single-item component.[29] The second most commonly utilized instrument was the Comprehensive Geriatric Assessment (CGA) (n= 4), followed by the Deficit Accumulation Index (DAI) (n=2). A summary of the results from each study[11,12,16,17,21–40] and the instrument utilized is provided in Table 2.

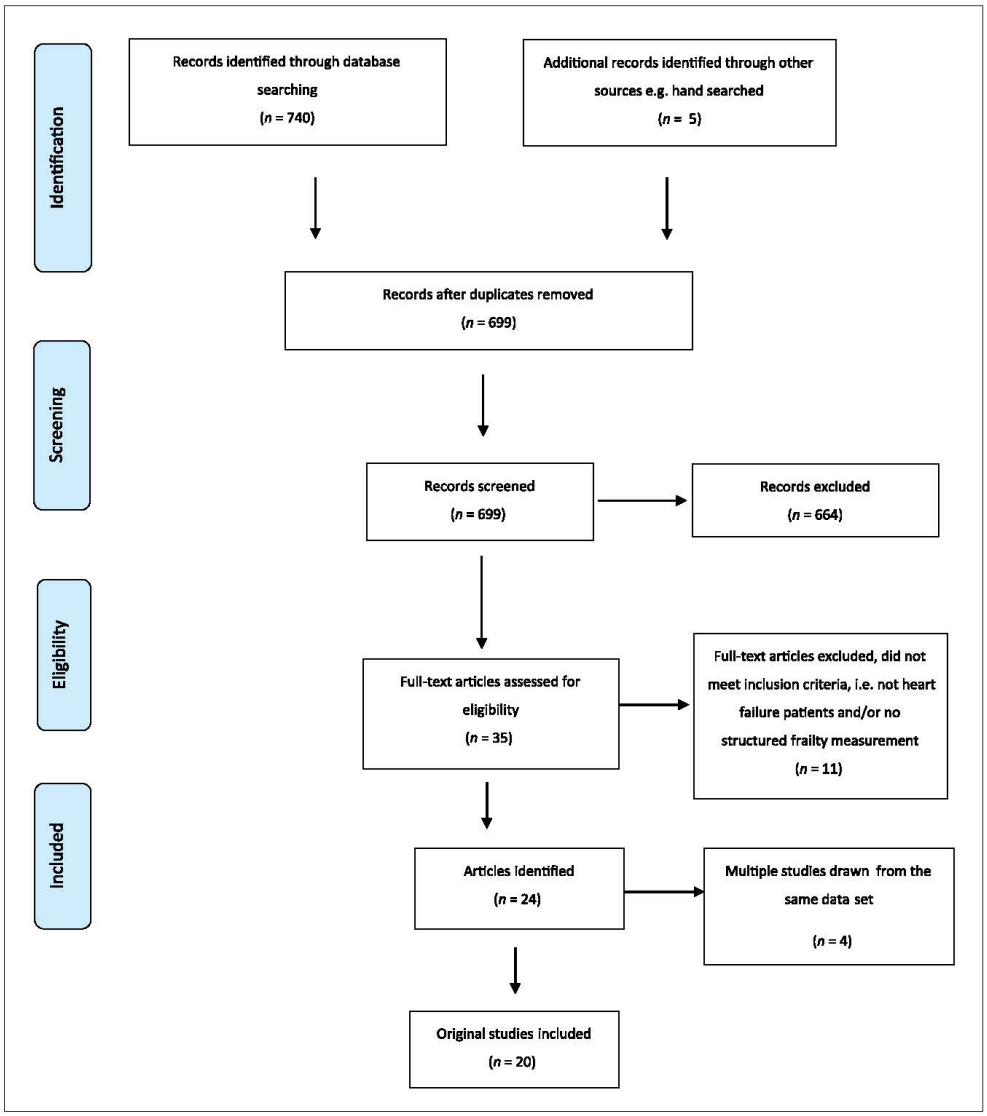

Figure 1. PRISMA flow diagram.

Discussion

Frailty assessment instruments identified

The FP. The FP defines frailty as a biological syndrome that causes age related physical decline. This scale focuses on five physical components of frailty (exhaustion, physical inactivity, walking speed, grip strength, and weight loss[41]) and was first developed as part of the Cardiovascular Health Study.[42] The FP has become one of the most well-known definitions, and is consistently identified as the most commonly used measure throughout the literature.[43] Whilst it has been used in numerous heart failure

Table 2. Summary table of articles reviewed.

Author/Year	Objective	Participants/setting	Design	Instrument	Domains	Results	JBI Score
Abou-Raya and Abou Raya (2009)[21]	To evaluate the association between osteoporosis and CHF	137 participants (83 CHF and osteoporosis, 54 control) Outpatient clinic	Case control	FP (modified)	Physical: weight loss, exhaustion, walking speed and HGS	CHF group: mean age 69.9 ± 4.5 years 51% were female Control group: mean age 70.1 ± 3.9 years 52% were female CHF group: *Frail* = 29% *Pre-frail* = 43% *Not frail* = 28% Control group: *Frail* = *nil* *Pre-frail* = 46% *Not frail* = 56% Levels of IL-6 and TNF-a significantly higher in CHF group compared with controls (p= 0.001 and p=0.005)	6/10
Altimir et al. (2005)[30]	To describe the degree of frailty in patients treated in a HF clinic and to evaluate age and sex differences	360 participants Outpatient HF clinic	Cross sectional	CGA (Barthel Index, OARS scale, Pfeiffer test, geriatric depression scale and social interview)	Physical/functional: Barthel Index of Activities of Daily Living and OARS scale; cognitive: Pfeiffer test; psychosocial: depression and social interview	Mean age 65.2 ± 10.9 years 74% were female *Frail* = 42% Frailty was strongly associated with anaemia (p<0.001) and diabetes (p=0.002) Abnormal Pfeiffer cognitive test found in 8% of patients Frailty also strongly correlated with number of hospital admissions	8/9
Boxer et al. (2008)[22,23,27]	To identify relationships between anabolic hormones, inflammatory markers and physical function	60 participants Outpatient university HF programme	Cross sectional	FP (modified)	Physical: weight loss, exhaustion, walking speed, physical activity level and HGS 6MWT	Mean age 78±12 years 28% were female *Frail* = 25% *Pre-frail* = 45% *Not frail* = 28% 48% had low free testosterone, 77% had low DHEAS and 30% had low vitamin D Higher FP score was correlated with higher hsCRP, higher IL-6 and lower vitamin D (all p<0.05)	7/9
Boxer et al. (2010)[24]	To determine if HF contributes to the development of functional decline and frailty	20 participants Outpatients	Follow-up of participants from a previous observational study	FP (modified)	Physical: weight loss, exhaustion, walking speed, physical activity level and HGS 6MWT	There were no changes in frailty/endurance status over time Deaths occurred in 18% on the NF/NE group 6MWT and frailty were each associated with mortality	8/9

Table 2. (Continued)

Author/Year	Objective	Participants/setting	Design	Instrument	Domains	Results	JBI Score
Buck and Riegel (2011)[31]	To determine if frailty explains the variability of HRQL in older adults with HF	130 participants	Secondary analysis	Novel frailty instrument used	Age, comorbidities (Charlson index), symptom severity (fatigue, dyspnoea on exertion and chest pain)	Median age of 72 years Frailty negatively impacts HRQL in older adults with HF	8/9
Cacciatore et al. (2005)[12]	To examine the predictive role of frailty in predicting on long-term mortality in subjects with CHF	1259 participants (120 with CHF and 1139 without) Outpatients	Case control	Frailty staging system	Disability, mobility, cognitive function, visual function, hearing, urinary continence and social support	CHF group: mean age 75.9 ± 6.7 60% were female CHF group: *Frail = 15%* Death progressively increased with frailty in subjects with or without CHF	8/10
Chung et al. (2014)[29]	To establish the predictive value of hand grip strength as a marker of frailty in VAD patients	72 participants Pre-operatively	Observational cohort	Hand grip strength	HGS measured pre VAD implant and monthly for six months post	Mean age of patients 59 ± 2 years *Frail* = 22% *Not frail* = 78% Low HGS correlated with low albumin levels Baseline HGS was lower in patients who died post VAD implant Patients with HGS <25% of body weight had significantly higher rates of bleeding postoperatively (54% *vs.* 17%, p= 0.002) and higher infection rates (85 *vs.* 54%, p=0.012)	8/9
Dominguez-Rodriguez et al. (2015)[32]	To assess the impact frailty status has on post implantation outcomes after CRT-D	102 participants	Prospective cohort	FP	Physical: weight loss, exhaustion, walking speed, physical activity level and HGS Barthel Index also collected as additional measure	Mean age 73 ± 3 years 53% were male *Frail = 28%* *Not frail* = 72% Frail patients had significantly higher rates of dyslipidaemia (66% *vs.* 41%, p= 0.026) No significant difference in hospital stay between frail and non-frail More frail patients experienced decompensated HF after CRT-D implantation than non-frail patients (51.7% *vs.* 16.4%, p= < 0.001)	9/11
Dunlay et al. (2014)[33]	Assess the post-operative outcomes associated with frailty in patients undergoing LVAD implantation as DT	99 participants	Observational	DAI	Index based on 31 deficits related to: self-care, activities of daily living, medical conditions, comorbidities and depression	Mean age 65.1 ± 9.4 years 82% were male *Frail = 34%* *Intermediate frail = 33%* *Not frail = 32%* One year mortality rates were 16.2%, 21.2% and 39.9% (p= 0.007) for not frail, intermediate frail and frail respectively	8/9

(Continued)

Table 2. (Continued)

Author/Year	Objective	Participants/setting	Design	Instrument	Domains	Results	JBI Score
Ferguson et al. (2016)[25]	To describe the clinical characteristics of patients admitted to hospital with CHF and atrial fibrillation	137 participants Inpatients	Prospective observational	SHARE Frailty index (modified FP)	Five physical domains of frailty: appetite, exhaustion, walking speed, physical activity level and HGS	Mean age 72±16 65% were male 92 participants had frailty assessed *Frail = 63%* Being frail and having higher comorbidity was associated with not receiving anticoagulant drugs at discharge	8/9
Gastelurrutia et al. (2013)[34,35]	Assess the relationship between fragility and QoL perceptions in HF	1405 participants 1314 participants[35] Outpatients	Observational	CGA	Physical/functional: Barthel Index of Activities of Daily Living and OARS scale; cognitive: Pfeiffer test; psychosocial: depression and social interview; QoL: Minnesota living with HF questionnaire	Mean age 66.7 ± 12.4 years 72% were male *Frail = 44%* The mean QoL score was 39.0 ± 18.9 for frail patients and 25.3 ± 17.1 for non-frail patients ($p < 0.001$)	8/9
Jha et al. (2016)[26]	To determine the prevalence of frailty in patients referred for heart transplantation	120 participants Hospital inpatients and outpatients seen in HF clinic	Observational	FP (modified)	Five physical domains: appetite, exhaustion, walking speed, physical activity level and HGS Cognitive and depression screening was also undertaken	Mean age 53 ± 12 years 69% were male *Frail = 33%* *Not frail = 68%* There was a significant difference in overall survival with more deaths occurring in the frail group ($p< 0.005$)	7/9
Lupon et al. (2008)[16]	To determine the impact of frailty and depressive symptoms on the one year mortality/ hospitalization rate of individuals with HF	622 participants Outpatient HF unit	Observational	CGA	Physical/functional: Barthel Index of Activities of Daily Living and OARS scale; cognitive: Pfeiffer test; psychosocial: depression and social interview	Median age 68 years 73% were male *Frail = 40%* Depressive symptoms found in 25% of participants One year follow-up: 60 participants (10%) had died and 101 (17%) had HF hospitalizations Presence of frailty was strongly associated with increased one year mortality (17% *vs.* 5% without frailty; $p<0.001$) Higher mortality in frail patients was observed in ≥70 years (20% *vs.* 8%; $p=0.003$) and in younger patients (13% *vs.* 3%; $p=0.001$) The presence of frailty was also associated with increased HF hospitalization (21% *vs.* 13%; $p=0.01$)	8/9

Table 2. (Continued)

Author/Year	Objective	Participants/setting	Design	Instrument	Domains	Results	JBI Score
Madan et al. (2016)[17]	To investigate the utility of frailty assessment in advanced HF	40 participants Outpatients in HF clinic	Single-centre pilot	FP (modified) 6MWT	Five domains: weight loss, exhaustion, walking speed, physical activity and HGS 6MWT	Mean age was 74.9 ± 6.5 years 58% were female *Frail = 65%* *Pre-frail = 35%* *Not frail = 0* There were more all cause hospitalizations in the frail *vs.* pre-frail group (p= 0.017) The 6MWT was not predictive of either of the primary end points and did not correlate to frailty score	7/9
McNallan et al. (2013)[11,36]	To determine the prevalence of frailty in a community cohort of patients with HF and to determine if frailty increases health care utilization	448 participants Outpatients Sub study of 223 patients[11]	Observational	FP (FP, DAI compared in sub study)	Five domains: weight loss, exhaustion, walking speed, physical activity and HGS	Mean age 73 ± 13 years 57% were male *Frail = 19%* *Intermediate frail = 55%* Frailty was associated with a 92% increased risk for ED visits and a 65% increase for hospitalizations *In the sub study[11] the FP and DAI were correlated and both equally predicted mortality*	8/9
Mlynarska et al. (2016)[37]	To establish the degree of frailty in patients with advanced HF receiving CRT	106 participants (74 de novo CRT and 32 upgrade CRT)	Prospective cohort	CSHA-CFS	Clinician rated frailty rating scale Domains: physical activity level, disability/dependence on others, comorbidity, activity level	Mean age: 74.9 ± 6.3 Frailty syndrome was found in: De novo group: *Frail = 82%* Upgrade group: *Frail = 69%* Total cohort: *Frail= 78%* The average of values of the CSHA-CFS were higher in the de novo group compared with the upgrade group (p= 0.027)	8/9

(Continued)

Table 2. (Continued)

Author/Year	Objective	Participants/setting	Design	Instrument	Domains	Results	JBI Score
Newton et al. (2016)[28]	To provide an insight into the acute HF admissions in New South Wales W and the Australian Capital Territory	Convenience sample 811 patients Inpatients	Prospective audit	SHARE Frailty Index (modified FP)	Five physical domains of frailty: appetite, exhaustion, walking speed, physical activity level and HGS	Mean age 77 ± 13 years 58% were male 557 participants underwent a frailty assessment *Frail* = 71% *Pre-frail* = 21%	8/9
Pulignano et al. (2010)[38]	To determine which patient's benefit mostly from DMP, according to their frailty profile	173 participants (73 DMP and 87 usual care) Outpatient HF clinic	Randomized control trial	CGA	Physical/functional: Barthel Index of Activities of Daily Living and OARS scale; cognitive: Pfeiffer test; psychosocial: depression and social interview	**DMP group:** Mean age 74.4 ± 5.9 51% were male **Usual care group:** Mean age 75.5 ± 5.7 53% were male *Frail* = 79% *Not frail* = 21% The DMP intervention was more cost-effective in moderately frail patients than usual care	8/13
Vidan et al. (2014)[39]	To evaluate clinical outcomes (death and rehospitalization), functional evolution, QoL and use of social resources in elderly patients hospitalized for HF	450 participants Consecutive elderly patients hospitalized for HF	Observational cohort	FP	Five domains: weight loss, exhaustion, walking speed, physical activity and HGS	Mean age 80 ± 6 years 49.6% were female *Frail: 70%*	8/9
Uchmanowicz et al. (2015)[40]	To evaluate the correlation between frailty and self-care abilities in HF patients	110 participants Inpatients	Observational	Tilburg Frailty Indicator	Socio-demographic characteristics and potential determinants of frailty collected by clinicians and 15 self-reported questions divided into three domains: physical, psychological and social	Mean age of cohort was 66 ± 11 years 54% were female *Frail* = 76% *Not frail* = 25% Longer duration of HF correlated with increased frailty Social components of the Tilburg Frailty Indicator were associated with the ability to self-care	8/9

CHF: chronic heart failure; FP: Frailty Phenotype; HGS: hand grip strength; IL-6: Interleukin 6; TNFa: tumour necrosis factor alpha; HF: heart failure; CGA: Comprehensive Geriatric Assessment; OARS: Older Americans Resource and Services; 6MWT: Six Minute Walk Test; DHEAS: dehydroepi-androsterone sulphate; hsCRP: high sensitivity C-reactive protein; NF/NE: ; HRQL: health related quality of life; VAD: ventricular assist device; LVAD: left VAD; CRT-D: cardiac resynchronization therapy defibrillator; DT: ; QoL: quality of life; ED: emergency department; DAI: Deficit Accumulation Index; CRT: cardiac resynchronization therapy; DMP: Disease Management Program; CSHA-CFS: Canadian Study of Health and Ageing Clinical Frailty Scale; NF/NE: Non-frail/Normal endurance; DT: Destination Therapy.

studies, the definition was originally validated in community dwelling older adults. The FP consists of a series to be performed by a clinician. These include: measurement of hand grip strength as assessed by a dynamometer and a five-metre gait speed test alongside self-reported measures regarding weight loss, exercise tolerance and physical activity.

Whilst the FP is the most commonly used instrument, it has been questioned whether all five domains of the FP are necessary, or whether a single measure is equally effective.[44,45] Reduced hand grip strength and five-metre gait speed have been recommended as predictive single-item measures of frailty.[1] Frailty instruments that measure multiple domains are often time consuming to complete and as such may not be feasible in a time constrained, acute clinical environment. Therefore, the use of a single-item measure may be more appropriate. Using hand grip strength as a measure of frailty in a cohort of individuals with heart failure undergoing ventricular assist device (VAD) implantation demonstrated that individuals with reduced hand grip strength pre VAD implant had higher rates of post-operative complications and lower survival rates. The use of hand grip strength was favoured over a full functional assessment in this cohort due to their minimal tolerance to undertake physical exertion and their disease related deconditioning, which is common in heart failure patients.[29] A limitation of hand grip strength as a single measure is that there may be certain individuals who are unable to perform a hand grip strength measurement, such as: those with hemiplegia, individuals unable to follow commands due to advanced dementia or other cognitive illness, those post sternotomy or permanent pace maker insertion and individuals with altered level of consciousness.

Modified FP. A number of studies included in this review used a form of modified FP.[21,22,26] All the versions of the FP used in these studies have variations from the original FP, such as using self-reported measures of appetite in place of weight loss[26] or altering the distance of the walk speed test.[21] These modified versions of the FP have not been validated for routine use in heart failure.

The SHARE Frailty Index (modified FP). The SHARE Frailty Index (SHARE-FI) was developed as part of Survey of Health Ageing & Retirement in Europe[46] and consists of variables relating to the five domains of the FP. It was designed to offer a valid alternative to the FP in the European context and aimed to facilitate the rapid assessment of frailty in the primary care setting.[47] It was validated in a cohort of community dwelling adults and provides a gender-specific frailty class. It is relatively similar to the FP, with the exception of weight loss and slowness, the 'weight loss' criteria being replaced with self-reported measures related to appetite and the 'slowness' component assessed using questions regarding functional limitation rather than the five metre gait speed test.[5,47] The SHARE-FI has been piloted in various clinical settings[48] but has only had very limited use in heart failure[25,28] and is currently not validated for routine use in this group.

The CGA scale. The CGA was first developed by Marjory Warren in the 1930s[49,50] as a method of structured assessment of an elderly person's psychosocial, medical, functional and environmental needs in an attempt to improve their treatment and follow-up plans.[51] The modern CGA involves the use of previously validated geriatric scales, that is, the Barthel Index of Activities of Daily Living,[52] the Older Americans Resource and Services (OARS) scale,[53] the Pfeiffer cognitive test[54] and the Yesavage geriatric depression scale.[55] The use of the CGA is highly cited in the literature, particularly in the cancer care specialty.[56–58]

The CGA has been validated for use as a frailty measurement tool in the general geriatric population[59] and has consistently demonstrated reliability for measuring frailty in various heart failure populations.[16,30,34] It provides a multidimensional team approach to measure functional, social and cognitive domains of frailty,[13] including disability and comorbidities, which have otherwise been acknowledged as related yet independent syndromes. The CGA and the FP both include self-reported patient questions and multiple assessments and, as such, may be considered too time intensive for routine use in the clinical setting.

The DAI. The DAI (also known as the Frailty Index) conceptualizes frailty as an accumulation of deficits. The DAI[60] was developed using data from the Canadian Study of Health and Ageing[61] and includes the assessment of multiple variables, including: 1) self-care ability; 2) dependence on assistive devices; 3) medical conditions; 4) body mass index and; 5) depression. It is designed so that many of the variables can be extracted from the patient medical records, therefore, the DAI may be more appropriate for the time-poor clinician. The benefit of the DAI over the FP is that it assesses various domains of human functioning, as opposed to only physical domains. In the context of heart failure, the DAI has been used in preoperative adults (mean age 65 years) undergoing left VAD implantation as destination therapy[33] and in a cohort of community dwelling older adults (mean age 71 years)[11] with a combined total of 222 patients. The DAI demonstrated correlation with the FP and was equally able to predict mortality[11] in a heart failure population. It is yet to be formally validated for use in heart failure.

Tilburg Frailty Indicator. The Tilburg Frailty Indicator (TFI) is based on a definition that frailty is a consequence of a combination of life course determinants and diseases leading to a decline in various domains of physical, psychological and

Table 3. Mapping of core domains to frailty instruments.

Frailty instruments cited in review articles	Physical function/ mobility	Self-reported physical activity level	Weight loss and/or weight measurement	Self-reported exercise tolerance or exhaustion	Appetite	Cognition	Other (social, comorbidity, depression, demographic, sensory)
Frailty Phenotype	X GS HGS	X	X[a]	X			
Deficit Accumulation Index	X		X			X	X
Tilburg Frailty indicator	X HGS[a]		X[a]	X		X	X
Comprehensive Geriatric Assessment	X					X	X
Frailty Staging System	X					X	X
Canadian Health and Ageing Clinical Frailty Scale	X						X
SHARE Frailty Index	X HGS	X		X	X		

[a]Self-reported.
GS: gait speed; HGS: hand grip strength.

social functioning which ultimately causes adverse outcomes such as disability, health care utilization and death.[62] The TFI consists of two parts: the first comprises variables related to the socio-demographic characteristics of the participant and the second comprises 15 self-reported questions divided into physical, psychological and social domains.[40] The TFI has previously demonstrated validity and reliability in a cohort of 484 community-dwelling persons aged 75 years and older.[62] It has not yet been validated for use in a heart failure population.

Frailty Staging System. The Frailty Staging System (FSS) was modified from a previous examination method used to assess elderly patients for functional disability.[63] It shortens the original 15 target areas down to seven core domains of functioning: disability, mobility, cognitive function, visual function, hearing function, urinary continence and social support.[12] The FSS has not been validated in a heart failure population.

Canadian Study of Health and Ageing Clinical Frailty Scale. The Canadian Study of Health and Ageing Clinical Frailty Scale (CSHA-CFS) is a seven point frailty scale that was applied to 2305 individuals aged greater than 65 years who participated in the second stage of the CSHA.[61,64] CSHA-CFS is a frailty rating score and ranges from *Very Fit* to *Severely Frail*. Whilst the CSHA-CFS was able to provide predictive information regarding mortality or the need for institutionalization in this group,[64] it has limited applicability to the heart failure population and has yet to be validated in this group.

There are several different instruments used to assess frailty in individuals with heart failure. However, to date none of these have been formally validated for use in this population. Due to the lack of validated frailty instruments in previous heart failure clinical research, caution should be exercised when interpreting the rates of frailty as they may be over or underestimated. This review has also demonstrated the inconsistencies in frailty assessment and the focus on physical frailty over multi-domain assessment in heart failure. Similar inconsistencies have been found in other areas of cardiovascular disease including, valvular heart disease.[65] The majority of studies included in this review have assessed frailty in community dwelling individuals or outpatients with heart failure, rather than inpatients, therefore there is insufficient data for comparison and there is no consensus about which time-point is most appropriate. Heart failure has been reported to be the most common cause of hospital admission in the elderly,[66,67] therefore, an opportunity exists for frailty screening to be undertaken within this large number of patients whilst they are hospitalized. This does, however, raise the question of what happens to frailty over time and whether an individual's frailty status changes when they are acutely unwell as opposed to post discharge. The hypothesis that an individual's frailty status would be worse when they are acutely unwell, and therefore it may be inappropriate to measure at this stage, has yet to be tested in the heart failure population.

The frailty domain most commonly assessed in this group is physical function/mobility. All seven frailty instruments include a question regarding physical function and three instruments include an objective gait speed test or hand grip strength measurement. An overview of the various domains of frailty that are assessed in each instrument is provided in Table 3.

Individuals with heart failure often experience disease related deconditioning and decreased exercise tolerance

which may be worse at periods of acute decompensation and hospitalization;[9] during this time it may affect their ability to perform a physical assessment and/or hand grip strength measurement. The duration of hospitalization should also be taken into consideration, that is, if the hospitalization was only one or two days, would this affect the accuracy of the frailty measurement less compared with a longer hospitalization of greater than seven days? An individual's appetite may also be difficult to assess when they are acutely unwell and hospitalized due to the disruption of their normal dietary habits. Furthermore, questions related to unintentional weight loss may also be difficult to assess in heart failure as individuals are often fluid overloaded, leading to frequent changes in weight.

To the authors' knowledge, this is the first review that has focused on the frailty assessment instruments in heart failure and the first to provide an overview of the most frequently assessed domains of frailty in this population. It is hoped that this review will help to guide future research and clinical practice in the most appropriate instrument and domains to address when assessing frailty in heart failure.

Conclusion

The assessment of frailty in heart failure is an emergent research priority and is often used as an important prognostic indicator in the clinical setting. This review has highlighted the need for a validated and clinically relevant frailty assessment instrument for use in a heart failure population. Further research is also needed to gain consensus on the most appropriate time to assess for frailty in this group and to elucidate whether there are significant differences in inpatient or outpatient assessment. The impact that disease related deconditioning or progression of heart failure symptoms may have on frailty assessment also needs to be explored in future research and the most reliable frailty domains for assessment should be chosen. Routine assessment of frailty as part of a holistic treatment plan for heart failure patients should be considered. Nurses are well placed in the acute and primary health care setting to undertake this assessment. It is imperative that frailty is being accurately and precisely assessed in this group with a validated instrument.

Implications for practice

- There are no validated frailty instruments available for use in heart failure.
- This review identifies that all frailty instruments assess physical function or mobility.
- Potential exists for routine frailty screening in heart failure in combination with other standardized methods of assessment.
- Nurses are appropriately skilled to undertake this screening as part of physical assessment and this is a fertile area for future research.

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Evaluating the convergent and discriminant validity of three versions of the frailty phenotype in heart failure: results from the FRAME-HF study

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Abstract

Background: Frailty is an important predictive measure of mortality and rehospitalisation in people with heart failure. To date, there are no frailty instruments validated for use in people with heart failure.

Aim: The aim of this study was to evaluate the convergent and discriminant validity of three versions of the frailty phenotype in those with heart failure.

Methods: A single site, prospective cohort study was undertaken among individuals with a confirmed diagnosis of heart failure. Frailty was assessed concurrently using three versions of the frailty phenotype: the original frailty phenotype and two modified versions; the Survey of Health, Ageing and Retirement in Europe frailty instrument (SHARE-FI) and the St Vincent's frailty instrument. Convergent and discriminant validity were assessed by reporting the correlations between each version and related heart failure subconstructs, and by evaluating the ability of each version to discriminate between normal and abnormal scores of other physical and psychosocial scales specific to heart failure-related subconstructs.

Results: The New York Heart Association classes were moderately correlated with the St Vincent's frailty instrument (r=0.47, $P \leqslant 0.001$), SHARE-FI (r=0.42, $P \leqslant 0.001$) and the frailty phenotype (r=0.42, $P \leqslant 0.001$). The SHARE-FI and the St Vincent's frailty instrument were both able to discriminate consistently between normal and abnormal scores in three out of five of the physical and psychosocial subconstructs that were assessed. The SHARE-FI was also able to discriminate between inpatients and outpatients who were classified as frail.

Conclusions: Both the SHARE-FI and the St Vincent's frailty instrument displayed good convergent and discriminant validity.

Keywords

Frailty, heart failure, frailty phenotype, frailty assessment

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Introduction

Frailty is a complex clinical syndrome associated with an increased vulnerability to acute stressors.[1,2] Frailty is strongly associated with heart failure (HF) and is a predictor of poor health outcomes including hospitalisation and mortality.[3,4] Frailty and HF share common underlying pathophysiological mechanisms. Both are associated with higher levels of circulating inflammatory cytokines, and both exhibit common symptomatology of exhaustion and decreased exercise tolerance. Cognitive impairment, depression, sarcopenia and cachexia are also common in HF and frailty.[5]

There is high variation in the prevalence of frailty in HF ranging from 15% to 79%. This large range in prevalence rate may be due to a number of factors including study population, timing of assessment in the illness trajectory as well as which instrument was used.[6] To date, there are no validated frailty assessment instruments for use in people with HF; this could explain the significant measurement heterogeneity, and hence variability in classifications of frailty. A recent systematic review identified seven frailty instruments that have been utilised in HF studies.[6] The most commonly used instrument was the frailty phenotype (FP), which defines frailty as a syndrome of increased vulnerability to acute stressors, causing age-related physical decline.[2,6] Despite being frequently used to assess frailty in people with HF, the validity and feasibility of this instrument for use in those with HF have yet to be determined. There are also many modified versions of the FP used in HF, but the validity of these modifications is also unclear.[6]

To date, there has been a focus on physical frailty in HF.[6] Therefore, we sought to focus on evaluating the validity of physical frailty instruments in this study. This study aimed to provide evidence of the convergent and discriminant validity of three different versions of the FP in adults with HF; the original FP,[2] the Survey of Health, Ageing and Retirement in Europe frailty instrument (SHARE-FI)[7] and the St Vincent's frailty instrument (SVF),[8] which are all measures of physical frailty. We hypothesised that in this cohort, those who were classified as frail would also score poorly in other physical and psychosocial subconstructs specific to HF, such as depression, poor physical performance and low quality of life.[9–11]

Methods

Study population and data collection

As part of the the FRAilty MEasurement in Heart Failure (FRAME-HF) study, participants aged 18 years and over with a confirmed diagnosis of HF were recruited from inpatient cardiology wards and the outpatient HF clinic of a quaternary referral hospital in Sydney, Australia. Non-English-speaking patients and those with diagnosed dementia or other cognitive impairment that prevented them from providing informed consent were excluded. Participants were recruited from August 2016 through to February 2018. Written informed consent was obtained at the time of enrolment for all participants. The study protocol was approved by the relevant human research ethics committees conforming to the principles outlined in the Declaration of Helsinki.[12] Sociodemographic and clinical information was collected at enrolment. Frailty was assessed concurrently at baseline using the original FP, the SHARE-FI and SVF. The items from the three versions were combined and randomly allocated to four different item orders, and each combination was randomly assigned to participants. Participants completed the self-reported questions from each version of the FP in the randomised order (16 questions in total), and the study nurse conducted the handgrip test and the 5-metre gait test. To complete both the self-reported frailty questions and the objective measures for all versions took less than 10 minutes.

Study measures

The frailty phenotype. The FP was conceptualised in 2001 from the Cardiovascular Health Study by Fried and colleagues to identify the subset of older adults at high risk of the adverse health outcomes clinically associated with 'frailty'.[2] This landmark study identified five domains of physical functioning that underpinned the syndrome of frailty: (a) unintentional weight loss (weight loss of $\geq$10 lb in the prior year); (b) weakness (decreased or weakened grip strength); (c) exhaustion (fatigue or declining endurance); (d) slowness (slower walking pace); and (e) low physical activity ($<$383 Kcal expended per week for men and $<$270 Kcal expended per week for women; as per the shortened Minnesota leisure time activities questionnaire.[13] Those who were positive in three or more domains are considered frail, those who are positive in one or two domains are classified as pre-frail, and those who are negative in all domains are classified as non-frail.[2]

The Survey of Health, Ageing and Retirement in Europe frailty instrument. The SHARE-FI was adapted from the FP as an alternative for use in a primary care setting and uses the same five phenotypic criteria, except for the unintentional weight loss domain; the SHARE-FI replaces the weight loss item with a question related to appetite. This study involved the assessment of 31,115 community-dwelling elderly individuals across 12 European countries.[7] Handgrip strength is collected using two consecutive measurements taken from the left and right hands. The highest of the four values is added to the algorithm. While the SHARE-FI also categorises individuals as frail, pre-frail and non-frail, these categories are determined by an algorithm rather than the simple classification mentioned above for the FP. The SHARE-FI has been used in several HF studies.[14–16]

St Vincent's frailty. The SVF is also modified from the original FP for the advanced HF population; it assesses the same five criteria as the original FP but replaces unintended weight loss with the change in appetite question from the SHARE-FI. This question also reduced the recall time from 12 months to 3 months. The shortened Minnesota leisure time activities questionnaire from the FP is replaced with the physical inactivity question from the SHARE-FI but with a shorter recall time (one week vs. one month). The SVF has been shown to be predictive of increased mortality in those undergoing heart transplantation.[8]

The Montreal cognitive assessment. The Montreal cognitive assessment (MoCA) version 7.1 was used to assess cognition.[17] The MoCA assesses cognitive functioning in the areas of visuospatial/executive thinking, naming, memory, attention, language, abstraction, delayed recall and orientation.[17] The MoCA has been shown to be sensitive for the detection of mild cognitive impairment (MCI) in heart failure patients.[18] A score of less than 26 out of 30 was considered abnormal and indicative of MCI.

Depression in medical illness-10. The depression in medical illness (DMI-10) questionnaire was used to assess depression in those with a diagnosed medical illness. The DMI-10 was chosen for this study as unlike other common depression screening instruments; it does not measure fatigue or alterations in appetite which were being assessed by the frailty instruments in this study. A score of 9 or greater was indicative of depression.[19]

EuroQoL 5D-5L. The EuroQoL 5D-5L (EQ5D-5L) is a generic self-reported, quality of life instrument, comprising five questions with five possible response levels.[20] It also includes a visual analogue scale that asks participants to rate their 'health state today' from 0 to 100. The EQ5D-5L was chosen as it is brief and non-burdensome to complete and it includes self-reported items related to physical function, self-care and mood, which are all domains regularly assessed in many frailty instruments.[5]

Australian-modified Karnofsky performance scale. The Australian-modified Karnofsky performance scale (AKPS) is a validated scale that was modified for the Australian population in those receiving palliative care treatment.[21] The AKPS is an 11-point rating scale from 0 to 100 that assesses an individual's performance status across three dimensions: activity, work and self-care. The scale is clinician rated and scores individuals from 0 (dead) to 100 (normal; no complaints; no evidence of disease). The AKPS scale has also been shown to correlate with New York Heart Association (NYHA) class.[22] For this study, we considered a score of less than 70 (cares for self, unable to carry on normal activity or active work) to be abnormal.

Statistical analyses

All statistical analyses were computed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Demographic and clinical characteristics were summarised using descriptive statistics; continuous data were summarised using means ± standard deviation for normally distributed data or median (interquartile range) for non-parametric data. Categorical variables were summarised using frequencies and percentages. For the group comparisons, the one-sample Kolmogorov–Smirnov test indicated that none of the continuous variables were normally distributed, these variables were dichotomised at the median.[23] Pearson's correlation coefficient was used to examine convergent validity and the chi-square test for discriminant validity. The threshold for statistical significance was a P value of less than 0.05.

Results

Study participants

A total of 131 participants was recruited and included in the analyses. Seventy-six per cent were men, with a mean age of 54 ± 14 years. Two-thirds were inpatients (65%) with the majority of those admitted for HF-related causes (93%). The majority reported English as their first language (94%) and three-quarters (76%) were of Caucasian background (Table 1).

Frailty prevalence

The frailty prevalence rates varied across the three versions, ranging from 33% to 54% being classified as frail, 31% to 54% being classified as pre-frail and 1% to 19% being classified as non-frail (Figure 1). There was no statistically significant difference between the prevalence of frailty between inpatients and outpatients (Figure 2). Of the five frailty domains measured according to the three versions, the weight loss/poor appetite domain was the most consistent across the FP, SVF and SHARE-FI instruments, with 41%, 53% and 49% of the cohort positive in this domain, respectively. The slowness domain was the least consistent, with the FP and SVF reporting that 15% and 27% were positive and the SHARE-FI reporting 77% positive in this domain. In the physical inactivity domain according to the SHARE-FI and SVF 34% were positive, while 86% were positive in this domain according to the FP (Figure 3).

Analysis of the five frailty domains according to inpatient or outpatient status revealed there was a statistically significant difference between those positive in the physical inactivity domain of the FP (90% inpatients, 78% outpatients; P=0.041) and between inpatients and outpatients who were positive in the slowness domain of the SVF (34% inpatients, 13% outpatients; P=0.012) (Table 2).

Table 1. Baseline characteristics.

Baseline characteristics, *N*=131	*N* (%), mean ±SD, median (IQR)
Age (years)	54 ± 14
Sex (male)	99 (76)
Inpatient	83 (65)
Length of stay days of inpatients	20 (12–35)
Caucasian background	100 (76)
English language	123 (94)
Heart failure-related hospitalisation	77 (93)
Medical history and clinical characteristics	
LVEF	31 ± 16
Myocardial infarction	32 (24)
Atrial fibrillation	70 (53)
Stoke	14 (11)
Hemiplegia	3 (2)
Chronic respiratory disease	18 (14)
Biochemistry	
Haemoglobin (g/L)	129 ± 25
Estimated glomerular filtration rate (mL/min/1.73 m^2)	62 ± 21
Creatinine (µmol/L)	108 (88–136)
Medications	
Beta-blockers	78 (66)
RAAS inhibition	97 (74)
Loop diuretics	103 (77)
Anticoagulants	76 (59)
Antiarrhythmics	48 (38)
Vitamin D	20 (16)
Physical and psychosocial characteristics	
Kcal expended per week (*n*=131)	0.00 (0.00–129)
Left hand grip strength (kg) (*n*=128)	30 ± 29
Right hand grip strength (kg) (*n*=129)	30 ± 12
5-Metre walk speed (s) (*n*=116)	5.1 ± 4.5
MoCA score (*n*=114)	26 ± 3
DMI-10 (*n*=123)	3 (1–12)

IQR: interquartile range; LVEF: left ventricular ejection fraction; RAAS: renin–angiotensin–aldosterone system; MoCA: Montreal cognitive assessment; DMI-10: depression in medical illness-10.

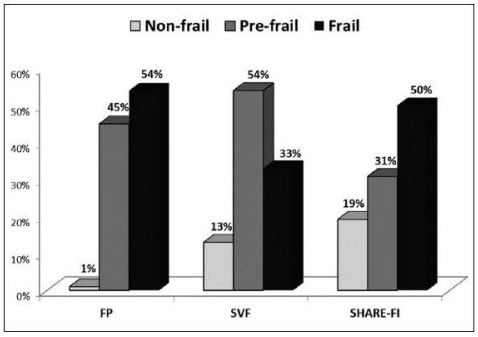

Figure 1. Frailty classifications according to instrument version.

Convergent validity

The correlations between the versions were highest between the SHARE-FI and SVF (r=0.64, $P\leq$0.001), followed by between the SVF and FP (r=0.51, $P\leq$0.001) and finally between the SHARE-FI and FP (r=0.45, $P\leq$0.001). The NYHA classes were moderately correlated with the SVF (r=0.47, $P\leq$0.001), SHARE-FI (r=0.42, $P\leq$0.001) and FP (r=0.42, $P\leq$0.001). Similarly, the AKPS scores were also moderately correlated with all three versions; SVF (r=0.43, $P\leq$0.001), SHARE-FI (r=0.39, $P\leq$0.001) and FP (r=0.24, $P\leq$0.001). All EQ-5D-5L dimensions were low to moderately correlated with each of the versions except for the anxiety and depression dimension, which was only correlated with the SVF. The DMI-10 and the MoCA score were also only correlated with the SVF.

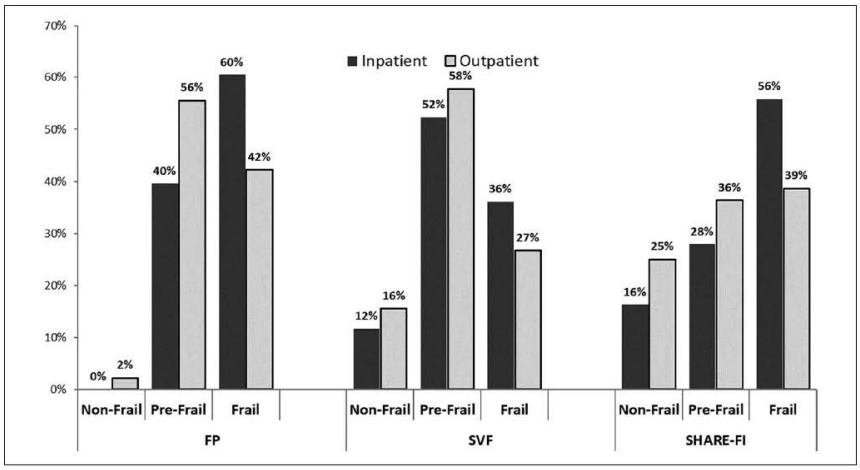

Figure 2. Frailty classifications of inpatients and outpatients according to instrument version.

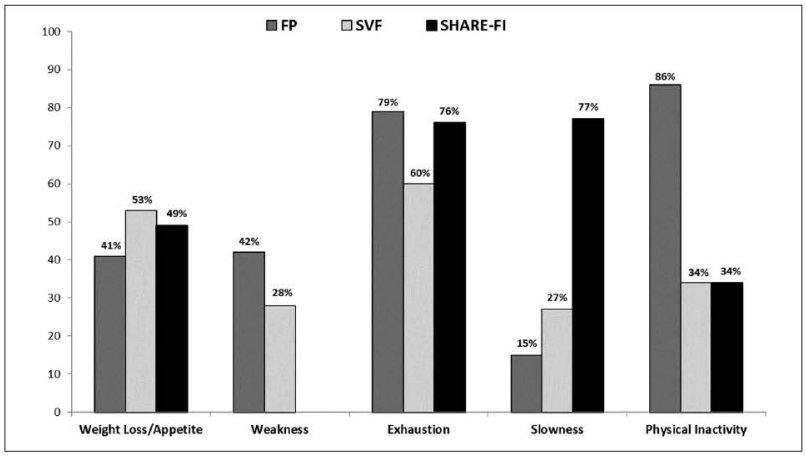

Figure 3. Proportion of those classified as positive in the five frailty domains according to frailty instruments.

Discriminant validity

Statistically significant group differences were detected between normal and abnormal AKPS, EQ5D-5L and DMI-10 scores within the three frailty categories (not-frail, pre-frail and frail) according to the SVF and SHARE-FI. The FP was only able to detect statistically significant group differences between normal and abnormal AKPS scores (Table 3). Both the FP (60% vs. 42%; P=0.067) and SHARE-FI (56% vs. 39%; P=0.170) were able to discriminate between inpatients and outpatients who were classified as frail (Figure 2).

Discussion

This study of three versions of the FP in people with HF showed that measurement heterogeneity exists within the same cohort, even when measuring the same frailty

Table 2. Proportion of inpatients and outpatients classified as positive in the five frailty domains according to three versions of the frailty phenotype.

	Weight loss/appetite			Weakness			Exhaustion			Slowness			Physical inactivity		
	n (%)	χ^2 (df=1)	*P* value	*n* (%)	χ^2 (df=1)	*P* value	*n* (%)	χ^2 (df=1)	*P* value	*n* (%)	χ^2 (df=1)	*P* value	*n* (%)	χ^2 (df=1)	*P* value
FP	37 (43)	0.470	0.465	38 (44)	0.158	0.691	67 (80)	0.271	0.603	15 (17)	1.400	0.237	78 (90)	4.161	0.041*
	16 (36)			17 (42)			36 (82)			4 (10)			35 (78)		
SVF	48 (56)	0.569	0.451	25 (29)	0.317	0.573	51 (59)	0.006	0.938	29 (34)	6.272	0.012*	28 (33)	0.119	0.730
	22 (49)			11 (24)			27 (60)			6 (13)			16 (36)		
SHARE-FI	44 (51)	0.379	0.538				70 (81)	2.863	0.091	69 (80)	0.946	0.331	28 (33)	0.119	0.730
	20 (46)						30 (67)			32 (73)			16 (36)		

df: degrees of freedom.
*Indicates statistical significance.
^Unable to calculate as variable is kept continuous.

Table 3. Group comparison analysis of the instrument version and abnormal scores of physical and psychosocial scales.

Clinical characteristics	Frailty category	FP (%)	χ^2 (df=2)	*P* value	SVF (%)	χ^2 (df=2)	*P* value	SHARE-FI (%)	χ^2 (df=2)	*P* value
Charlson index score (>2)	Frail	60	3.151	0.207	40	2.374	0.305	60	5.379	0.068
	Pre-frail	38			50			28		
	Non-frail	2			10			12		
MoCA score (up to 26)	Frail	57	1.535	0.464	33	0.976	0.614	48	0.214	0.899
	Pre-frail	42			58			31		
	Non-frail	2			9			21		
AKPS score (up to 70)	Frail	61	10.094	0.006*	40	11.066	0.004*	57	9.249	0.010*
	Pre-frail	40			50			28		
	Non-frail	1			11			16		
DMI-10 score (≥9)	Frail	60	1.296	0.523	37	7.327	0.026*	50	7.871	0.020*
	Pre-frail	40			63			44		
	Non-frail	0			0			6		
EQ5D-5L VAS (up to 60)	Frail	60	3.415	0.181	48	17.910	<0.001*	60	7.322	0.026*
	Pre-frail	40			40			28		
	Non-frail	0			12			13		

Pearson chi squared indicates statistically significant.*
MoCA: Montreal cognitive assessment; AKPS: Australia-modified Karnofsky performance scale; DMI-10: depression in medical illness-10; EQ5D-5L: EuroQoL5D-5L visual analogue score.

domains. Previous reviews of frailty in HF have reported large variance in the prevalence rate, and this difference is likely to be due not just to study design and population but to the frailty instrument chosen.[24,25] As this study has demonstrated, when using different versions of the same instrument, even minor modifications provide very different results. It is therefore important that studies identify not only the instrument used but also if a modified version has been used and any validation work of the modified instrument that was undertaken.

This study revealed that most of the frailty domains across the three versions were highly variable. The weight loss/appetite domain was the most consistent across the three versions. The FP uses a question related to weight loss of 'more than 5 kg of unintended weight loss in the previous 12 months', the SVF and SHARE-FI both use a question related to appetite. In this study, replacing the weight loss question with a question regarding appetite did not significantly alter the outcome in this domain and so would seem to be appropriate, particularly given the challenges of accurately assessing self-reported, unintended weight loss in HF. The slowness and physical inactivity domains displayed a floor and ceiling effect in each version, and therefore may not be appropriate for capturing those with HF who are positive in these frailty domains.

The slowness domain was the least consistent across the five frailty domains, with 15%, 27% and 77% positive in this domain according to the FP, SVF and SHARE-FI, respectively. The 5-metre walk test is used to measure slowness in the FP and SVF, but the result is calculated differently for both. There was 11% of the cohort who were unable to complete the 5-metre walk test. The majority of these were due to the patient being too unwell, and therefore unable to mobilise to perform the test. For analysis, those unable to complete the 5-metre walk test were given a point and assessed as positive in this domain. While walking speed as a measure of physical function has been used clinically across many health conditions, there is no advice guiding when it is clinically advisable for a person with HF to mobilise or refrain from attempting this test.[8,26,27] The clinical boundaries around performing the 5-metre walk test in HF need to be established. There were also significant differences detected between inpatients and outpatients who were positive in this domain according to the SVF (34% vs. 13%; P=0.012) but not with the FP (17% vs. 10%; P=0.237). The SHARE-FI replaces the 5-metre walk speed test with two questions related to an individual's ability to walk 100 metres or climb a flight of stairs without resting. This replacement question, while less burdensome for a participant to complete, is subjective and the ambiguous time frame may cause individuals to over or underestimate their abilities. The SHARE-FI slowness questions are also closely related to exercise capacity, which may be problematic in those with HF. With decreased exercise tolerance and shortness of breath intrinsic to HF,[28] asking someone with symptomatic HF if they have difficulty walking 100 metres or climbing a flight of stairs they are likely to respond 'yes', which could explain why 77% were positive in this domain according to the SHARE-FI. The benefit of the 5-metre walk speed test is that it allows the assessment of walking speed over a short distance. Those with HF will be likely to start a walking speed test at their normal pace but have to slow down or stop before they reach 100 metres. Therefore, the 5-metre walk speed test may provide better discrimination between slowness caused by frailty and slowness caused by HF.

To assess physical inactivity, the FP uses a 12-item shortened version of the Minnesota leisure time activity questionnaire, which asks the participant to recall the amount of time spent performing physical activities over the past 2 weeks, such as walking for exercise, jogging and tennis.[13] As more than two-thirds of our cohort were inpatients, many of whom were in hospital for more than 2 weeks at the time of assessment, it was difficult for participants to answer the questions, as most pertain to physical activities performed outside, making it impossible for people to complete these activities while hospitalised. We had responses from all participants, but only 45% of the cohort was able to answer that they had completed any of the physical activities listed on the questionnaire. Therefore, we were unable to calculate a mean Kcals expenditure per week result greater than 0. Consequently, 86% were positive in the physical inactivity domain according to the FP (90% inpatient vs. 78% outpatient; P=0.041). These results suggest that the Minnesota leisure time activity questionnaire has poor utility in HF, particularly in those who are hospitalised. There may be scope in future research to explore if modifying the activities listed may be more appropriate in HF or if wearable physical activity trackers could be more useful.[29]

This study showed that the two modified versions of the FP, the SVF and the SHARE-FI, displayed the strongest validity over the original FP. The SVF instrument correlated most highly with the other relevant HF subconstructs, displaying good convergent validity. The SHARE-FI also displayed good convergent validity with low to moderate correlation with the subconstructs assessed.

The SHARE-FI and SVF both displayed discriminant validity, with both versions able to detect significant group differences between the three frailty classifications (not-frail, pre-frail and frail) and abnormal scores in three out of five of the HF-related subconstructs. The FP was only able to detect significant group differences in one out of five of the subconstructs. The SHARE-FI was also able to discriminate between the inpatients and outpatients who were classified as frail; it was able to recognise that (as expected) those who were admitted to hospital at the time of frailty assessment had higher rates of frailty than those who were outpatients.

Strengths and limitations

The strengths of this study include the pragmatic design, which aims to improve the clinical applicability of these results, in the hope of standardising methods of assessment and interpretation. Some limitations also need to be considered. First, the sample we used is unique compared to other HF studies and may limit the generalisability of results; it was a younger cohort, reflecting the population of the study site, and the length of stay for those who were inpatients was considerably higher compared to other HF studies.[16, 30] The high prevalence of frailty in those with HF, despite the low mean age, is further evidence of the strong association between frailty and HF.

Conclusions

The SVF and SHARE-FI both displayed good convergent and discriminant validity, suggesting both versions are valid measures of frailty in those with HF. To the authors' knowledge, this is the first study to compare the validity of different versions of the FP in HF. These results need to be confirmed in a larger and more diverse HF cohort.

Implications for practice

- This study provides evidence of the convergent and discriminant validity of three versions of the frailty phenotype in those with heart failure.
- Frailty prevalence is highly variable even when using different versions of the same frailty instrument.
- When assessing frailty it is important to not only identify the instrument used, but if any modifications have been made, as even minor modifications can cause wide variations in prevalence rates.

Author contributions

All authors contributed to this current manuscript. All authors met the criteria for authorship and have given their final approval of the submitted manuscript.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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Frailty Assessment in Heart Failure: an Overview of the Multi-domain Approach

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Abstract

Purpose of Review The study aims (1) to provide a contemporary description of frailty assessment in heart failure and (2) to provide an overview of multi-domain frailty assessment in heart failure.

Recent Findings Frailty assessment is an important predictive measure for mortality and hospitalisation in individuals with heart failure. To date, there are no frailty assessment instruments validated for use in heart failure. This has resulted in significant heterogeneity between studies regarding the assessment of frailty. The most common frailty assessment instrument used in heart failure is the Frailty Phenotype which focuses on five physical domains of frailty; the appropriateness a purely physical measure of frailty in individuals with heart failure who frequently experience decreased exercise tolerance and shortness of breath is yet to be determined. A limited number of studies have approached frailty assessment using a multi-domain view which may be more clinically relevant in heart failure.

Summary There remains a lack of consensus regarding frailty assessment and an absence of a validated instrument in heart failure. Despite this, frailty continues to be assessed frequently, primarily for research purposes, using predominantly physical frailty measures. A more multidimensional view of frailty assessment using a multi-domain approach will likely be more sensitive to identifying at risk patients.

Keywords Frailty · Frailty assessment · Geriatrics · Heart failure · Multi-domain frailty assessment

Introduction

Globally, heart failure (HF) is a leading cause of mortality and a major driver of health care costs [1]. It is characterised by episodes of clinical deterioration and progressive symptoms, functional decline and ultimately death, despite optimal clinical management [2]. There has been major advancement in both the pharmacological and non-pharmacological management of HF. Yet, these advancements are associated with high costs and finite resources. The growing international attention on reducing rehospitalisation and length of stay in a bid to lower the overall economic burden of HF has resulted in the careful use of advanced therapies such as cardiac transplantation and device-based therapies, making the selection of the most appropriate candidates increasingly important. Frailty has been suggested as a suitable method to risk-stratify individuals and predict worse outcomes in HF, including rehospitalisation and death, which has sparked interest in frailty assessment, among clinicians and researchers alike [3].

Definition of Frailty

Frailty is a syndrome of increased vulnerability to acute stressors, including falls and hospitalisation and is associated with reduced physiological reserve across multiple body systems [4•]. Frailty is characterised by accelerated ageing and

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the failure of homeostatic mechanisms manifesting as significant vulnerability in those individuals who are frail. Those who are frail have a lower level of baseline functionality compared to those who are non-frail and when faced with a minor stressor event, such as an infection, frail individuals experience a prolonged deterioration and rather than returning to their baseline level of functioning, they deteriorate further toward dependence or disability. Conversely, individuals who are non-frail, when faced with a minor stressor event, only experience a short deterioration before returning to their baseline level of functioning [5••].

While there is a lack of agreed consensus upon the operational definition of frailty, there are two broad approaches to assess frailty [6]. The first defines frailty as a biological syndrome that causes age-related physical decline. This definition has been widely adopted since the development of the Frailty Phenotype by Fried and colleagues as part of the Cardiovascular Health Study [7]. The Frailty Phenotype defines someone as frail if they are positive in three or more out of the following five criteria: weak grip strength, slowed walking speed, unintentional weight loss, low physical activity and physical exhaustion [7]. This approach involves a combination of patient self-reported and clinician-assessed components and includes an objective measure of weight, walking speed and hand grip strength (as measured via a handgrip dynamometer). The second definition by Rockwood and colleagues defines frailty as a multidimensional syndrome that is assessed through the accumulation of health deficits across multiple domains, such as cognition, activities of daily living, comorbid diseases present or abnormal laboratory results [8, 9]. The Deficit Accumulation Index is expressed as the ratio of health deficits present to the total number of deficits assessed [10]. The number of health deficits used to assess frailty can vary and can be altered to suit a certain health population or clinical setting. The Deficit Accumulation Index is strongly associated with institutionalisation and death, particularly if more than 30 deficits are assessed [9]. A major difference between the Frailty Phenotype and the Deficit Accumulation Index is that the latter can be ascertained from the medical records rather than relying on patient self-reported and objective measures and therefore could be more suitable for assessing frailty in large cohorts [11].

In addition to the Deficit Accumulation Index, there are number of other valid and reliable instruments available that adopt a multi-domain view of frailty, such as the Tilburg Frailty Indicator [12] and the Edmonton Frail Scale [13]. A multi-domain view of frailty moves away from a purely physical definition and acknowledges that frailty is a multidimensional syndrome capable of causing deterioration across multiple domains of human functioning [14, 15]. Multi-domain instruments assess frailty across a broad range of domains, including physical function, disability, cognitive function and psychosocial health [16].

Frailty Assessment in Heart Failure

Frailty is highly prevalent in HF and is an independent predictor of worse outcomes, such as hospitalisation, non-adherence to guideline-based therapy and death [17–21]. Reported rates of frailty in HF range from 15 to 79% [22••]; the large variation in prevalence is likely due to the different populations studied, such as inpatients and community dwellers, varying time points in the illness trajectory at which assessment was undertaken and the wide variability in the frailty instruments used. Consequently, research regarding frailty in HF has significantly increased over the last decade and has resulted in the assessment of frailty being recommended by various international HF societies [23–26]. A recent systematic review of frailty assessment instruments in HF identified that 20 primary studies used seven unique assessment instruments (namely the Frailty Phenotype, the Deficit Accumulation Index, the Tilburg Frailty Indicator, the Comprehensive Geriatric Assessment [27], the Frailty Staging System [28], the Canadian Health and Ageing Clinical Frailty Scale [29] and the Survey of Health, Ageing and Retirement in Europe Frailty Index [30]), of these seven instruments, none have been validated for use in HF [22••]. Assessing frailty with a validated instrument has been recommended in international frailty guidelines [6, 31]. There is an urgent need for a validated frailty instrument for use in people with HF.

The most common assessment instrument used in HF is the Frailty Phenotype followed by the Comprehensive Geriatric Assessment (CGA) [22••]. The CGA is a robust form of holistic assessment and is a useful instrument for determining the medical, psychological, functional and environmental needs of older people [32]. The CGA has had modest use in HF frailty research (20% of HF studies [22••]); the amount used in the clinical setting for HF remains largely unknown. The CGA is used primarily for geriatric care and guides the development of treatment plans for older people and is designed to identify high-risk individuals [32]. If a person is classified as being frail, a CGA may be a useful adjunct to plan treatment and management.

Proposed Frailty Domains for Assessment in Heart Failure

Physical Frailty

Physical frailty is defined as a combination of weakness, slowness, shrinking, low physical activity and exhaustion which

manifests as a decrease in physiological reserve and failure of homeostatic mechanisms [5••, 7]. To date, frailty assessment in HF has been focused on physical frailty, with the majority of studies (55%, $n = 11$, of HF studies) using variations of the Frailty Phenotype as the assessment instrument of choice [22••]. The focus on a physical definition of frailty in people with HF is problematic with individual's often reporting symptom exacerbations, such as shortness of breath and decreased exercise tolerance, making the assessment of physical function difficult.

A likely component of physical frailty in advanced HF is cachexia. Frailty and cachexia both cause unwanted weight loss which can progress to extreme weakness and death [33]. Cachexia is considered a complex metabolic syndrome associated with underlying disease and manifests with excessive weight loss and disproportionate muscle wasting [34]. Cardiac cachexia is a term used to represent the terminal phase of body wasting often seen in the advanced stages of HF [35]. Sarcopenia, another muscle wasting disorder, is caused by age-related muscle loss rather than underlying disease [33]. The assessment of sarcopenia is similar to that of physical frailty: low muscle mass, low physical performance/slow gait speed and low muscle/grip strength [36]. Sarcopenia and cachexia are closely linked and are potential drivers of frailty; the relationship between these three interrelated, yet discrete syndromes, should be considered when assessing physical frailty in people with HF.

Cognitive Frailty

Cognitive frailty is a clinical syndrome of reduced cognitive reserve, excluding Alzheimer's disease or other dementias, characterised by the presence of coexisting physical frailty and potentially reversible cognitive impairment [37, 38]. Cognitive frailty is considered a potential precursor to neurodegenerative processes [39]. Screening for cognitive frailty using a comprehensive cognitive assessment, such as the Montreal Cognitive Assessment (MoCA), has been recommended [37, 40]. Cognitive impairment is common in HF with estimated prevalence ranging from 25 to 74% and is associated with increased risk of adverse outcomes, including disability and mortality [41, 42]. With the high prevalence of cognitive impairment in HF, it is imperative that cognitive frailty is adequately assessed in this group. The MoCA is a sensitive and clinically relevant screening tool appropriate for detecting mild cognitive impairment in HF [43]. Jha et al. recently demonstrated that the assessment of cognitive frailty in HF using the MoCA has increasing utility; the addition of cognitive domains to the frailty assessment in a cohort of 156 individuals with advanced HF significantly improved the predictive validity of 12-month survival ($p < 0.02$ for physical frailty alone vs $p < 0.002$ when cognitive assessment was added) [44]. The addition of cognitive assessment as part of a multi-domain approach to frailty in HF should be a high-priority theme for future research.

Multi-morbidity

Multi-morbidity is defined as the presence of two or more simultaneous chronic medical conditions [45]. Heart failure and frailty are both associated with advanced age and multi-morbidity [5••, 46]. In an Australian study of 6730 individuals (median age 84 years) with HF, 97% ($n = 6528$) were found to have at least one comorbid condition that could cause a treatment conflict and 55% ($n = 3702$) were found to have three or more comorbid conditions [47]. The recently proposed pragmatic framework to optimise health outcomes in HF and multi-morbidity recommends that a frailty assessment be undertaken when screening for multi-morbidity [48]. With such high rates of comorbidities present among individuals with HF, a frailty instrument that assesses multi-morbidity may be of value. A comorbidity index, such as the Charlson comorbidity index [49], may be useful when assessing frailty in HF. The Deficit Accumulation Index and the Comprehensive Geriatric Assessment both screen for multi-morbidity as part of the frailty assessment but have had limited use in HF research. The FRAIL (Fatigue, Resistance, Illnesses, and Loss of Weight) scale [50] is another example of a frailty instrument that assesses how many illnesses the patient has including hypertension, diabetes, cancer (other than a minor skin cancer), chronic lung disease, myocardial infarction, congestive heart failure, angina, asthma, stroke and renal disease. The benefits of the FRAIL scale are that it can be easily administered over the phone and is completely patient self-reported rather than clinician assessed. The FRAIL scale has not been validated in this population. With the growing focus on multi-morbidity, it is appropriate to include multi-morbidity screening as part of a multi-domain frailty assessment in HF.

Depression

Several studies assessing frailty in HF have used instruments that include domains related to mood, particularly depression [18, 19, 51]. Depression is common in HF with reported prevalence ranging from 13 to 78% [52]. A meta-analysis of depression in HF found that clinically significant depression was present in 22% of people and concomitant depression and HF associated higher rates of death, hospitalisation and emergency room visits [53]. In an observational study of 622 HF patients, 25% ($n = 156$) were found to have depressive symptoms. There were also significant associations between frailty (16.9 vs 4.8%; $p < 0.001$), depressive symptoms (15.3 vs 7.7%; $p = 0.006$) and 1-year mortality [54]. There are several frailty instruments that include measures related to depression and/or mood domains, such as the Deficit Accumulation Index, Comprehensive Geriatric Assessment and the Tilburg

Frailty Indicator. There are also previously validated depression screening tools, such as the Depression in Medical Illness scale [55], that have shown utility in HF when used in combination with another frailty instrument [44]. With high prevalence of depression in frailty and HF alike, it is appropriate for domains related to depression to be included when undertaking a multi-domain frailty assessment in those with HF.

Utility of Frailty Assessment in the Clinical Setting

Assessing frailty as part of a routine clinical assessment is becoming more common among some clinicians. In a recent survey of 388 clinicians across 44 countries, 53% of clinicians reported always assessing frailty in their routine clinical practice. Participants were mostly physicians (93%) working primarily in geriatrics (83%) [56]. The number of cardiovascular clinicians who undertake routine frailty assessment remains largely unknown; therefore, the utility of frailty as part of routine clinical care is also yet to be determined. The overwhelming interest in frailty and cardiovascular disease over the last decade could result in frailty assessment becoming part of the routine practice of cardiovascular clinicians, particularly those specialising in chronic cardiac conditions. Precisely how this routine frailty assessment will be achieved in an already time-pressured, resource-limited clinical environment is unknown, as is who is best placed to perform this assessment (e.g. occupational therapist, nurse or physician). As mentioned previously, the most common frailty instrument used in HF is the Frailty Phenotype, which focuses on purely physical domains of frailty and requires objective measures of gait speed and hand grip strength to be performed by a clinician. With the multitude of issues surrounding the focus on physical frailty and potential lack of appropriately skilled clinicians available to undertake these objective measures, a self-reported frailty assessment may be more appropriate. A recent large clinical trial in acute coronary syndrome assessed frailty using a patient self-reported questionnaire only version of the Frailty Phenotype [57]. The omission of the objective clinician-assessed measures could make this version of the Frailty Phenotype more appropriate for routine use in HF. However, the adoption of routine frailty screening for HF is still dependent on the availability of quick, easy-to-use and clinically relevant instrument; until this is established and trialled, it is difficult to estimate the true utility of frailty assessment in the clinical setting.

Interventions to Improve Frailty

To date, most frailty research has been focused on predicting adverse events or devising novel ways to measure frailty in different populations. There has been limited research regarding interventions for improving frailty. Randomised control trials that include interventions such as exercise programs/physical training and cognitive training, and nutritional support have been shown to be effective at improving frailty in older adults [58–60]; however, there have been limited recommendations for HF. The application of a physical exercise program for those with HF would need to be carefully tailored to suit people with poor exercise tolerance. It may be advantageous to ensure that HF symptoms are as adequately managed as possible before the commencement of any exercise program, although the unpredictable nature of HF may make this difficult.

While the interventions to improve frailty in HF are limited, Jha et al. recently showed that frailty was reversible in certain individuals with advanced HF who survived the early period post heart transplantation [61]. With the reversibility of frailty possible in some individuals with HF, there exists potential for the development of interventions to improve or reverse frailty in this population. Some suggested recommendations (for the geriatric population) from the recently published Asia-Pacific Clinical Practice Guidelines for the management of frailty [31] propose the following:

- Prescribing physical activity with a resistance training component
- Reducing polypharmacy
- Providing nutritional support (i.e. food fortification and protein/calorific supplementation) in those with unintended weight loss

These are in line with the recommendations from frailty consensus: a call to action [6] published over 4 years ago (also aimed at the geriatric population). There exists potential to examine the efficacy of the above interventions in HF and/or propose novel interventions; this should be a key area for future research.

Future Directions

Frailty has become a high-priority research theme in cardiovascular medicine, particularly for individuals with HF. While frailty as a comorbid syndrome has gained traction among HF clinicians, the recommendations surrounding assessment remain ambiguous. There is a strong focus on physical frailty domains rather than a multi-domain view of frailty. The degree of impact that a period of decompensated HF has on the assessment of physical frailty measures is yet to be determined and could be a fertile area for future research.

Frailty is primarily considered a geriatric condition due its association with age-related changes [5••]. However, in people with HF, frailty is often identified in younger individuals

as well. The prevalence of frailty was reported to be 22 and 33% in two reports of patients referred for heart transplantation or implantation of a ventricular assist device(s) with a mean age of 59 ± 2 and 53 ± 12 years respectively [62, 63]. With frailty also occurring in younger individuals with advanced HF, the origin of their frailty needs to be further examined. If the frailty is not due to age-related changes, it may be related to their advanced disease processes, i.e. 'disease-related frailty' as opposed to 'age-related frailty', effectively, making them 'biologically aged' rather than 'chronologically aged'. There is also a group of individuals that are frequently much younger, for example those waiting for heart transplantation or individuals with congenital heart disease who develop HF as adolescents. This specific group has chronic and often end-stage HF and if targeted in future research, it could potentially provide researchers the opportunity to differentiate between disease-related frailty and age-related frailty.

To date, the focus of frailty research in HF has been to investigate the utility of frailty as a predictor of worse outcomes; this has now been firmly established. International consensus on the most clinically relevant assessment approach needs to be reached and a validated instrument for this population is needed. Frailty needs to move from a being an interesting research variable to an important clinical instrument utilised as part of the management plan for individuals with HF. At that point, instead of merely predicting worse outcomes, frailty assessment can help prevent them.

Conclusion

There is a lack of consensus regarding the optimal way to assess frailty in HF and there are currently no validated assessment instruments available for use in this population. A multi-domain approach to frailty assessment that incorporates not only physical but cognitive, multi-morbidity and mood domains may be more clinically relevant and reliable for routine use in HF; however, further research is needed to confirm this hypothesis.

Compliance with Ethical Standards

Conflict of Interest Caleb Ferguson and Phillip J. Newton declare no conflicts of interest.

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- •• Of major importance

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Appendix 2: Modifications to the FRAIL scale used in FRAME-HF

FRAIL Scale	Modifications for FRAME-HF
Fatigue: "How much of the time during the past 4 weeks did you feel tired?" 1 = All of the time, 2 = Most of the time, 3 = Some of the time, 4 = A little of the time, 5 = None of the time. Responses of "1" or "2" are scored as 1 and all others as 0. Baseline prevalence = 20.1%.	"How often over the last week did you feel like everything was an effort?"
Resistance: "By yourself and not using aids, do you have any difficulty walking up 10 steps without resting?" 1 = Yes, 0 = No. Baseline prevalence = 25.5%.	'Do you have difficulty climbing a flight of stairs without resting'
Ambulation: By yourself and not using aids, do you have any difficulty walking several hundred yards?" 1 = Yes, 0 = No. Baseline prevalence = 27.7%.	"Do you have difficulty walking 100 metres"
Illnesses: For 11 illnesses, participants are asked, "Did a doctor ever tell you that you have [illness]?" 1 = Yes, 0 = No. The total illnesses (0–11) are recoded as 0–4 = 0 and 5–11 = 1. The illnesses include hypertension, diabetes, cancer (other than a minor skin cancer), chronic lung disease, heart attack, congestive heart failure, angina, asthma, arthritis, stroke, and kidney disease. Baseline prevalence = 2.1%.	(Collected from medical history data).
Loss of weight: "How much do you weigh with your clothes on but without shoes?	'Have you lost more than 5 kgs over the last year'

[Current weight]" "One year ago in (MO, YR), how much did you weigh without your shoes and with your clothes on? [weight 1 year ago]" Percent weight change is computed as: [[weight 1 year ago - current weight]/weight 1 year ago]] * 100. Percent change > 5 (representing a 5% loss of weight) is scored as 1 and < 5 as 0. Baseline prevalence = 21.0%

Appendix 3: The FRAME-HF case report forms

FRailty meAsureMEnt in Heart Failure (FRAME-HF)

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Subject ID | | | | | **Subject Initials** | | | |

Instructions: Shade circles like this: ● Not like this: ⊘ Please print in BLOCK STYLE in the boxes

Section 1 Patient Profile

Date of birth D D / M M / Y Y Y Y Age ◯Female ◯Male

Ethnicity _____ Main language spoken at home _____

Lives Alone ◯Yes ◯No Residential aged care facilty ◯Yes ◯No

Admission status ◯ Inpatient ◯Outpatient

Date of Admission D D / M M / Y Y Y Y Length of stay

Date of Discharge D D / M M / Y Y Y Y days

Cause of Admission ◯ CV ◯ Non-CV ◯ Not applicable

If CV related, is it HF? ◯Yes ◯No ◯Not applicable

Smoking status ◯Never smoked ◯Ex-smoker ◯Current smoker

Number of cigarettes smoked / day _____ Number of years smoking /ed for _____

Section 2 Charlson Index

◯ Myocardial infarction
◯ Congestive heart failure
◯ Peripheral vascular disease
◯ Cerebrovascular disease
◯ Dementia
◯ Chronic pulmonary disease
◯ Connective tissue disease
◯ Ulcer disease
◯ Mild liver disease
◯ Diabetes
◯ Hemiplegia
◯ Moderate or severe renal disease
◯ Diabetes with end organ damage
◯ Any tumor
◯ Leukemia
◯ Moderate or severe liver disease
◯ Metatastic tumor
◯ AIDS

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Section 3 Previous Medical History

	Has the patient had any of the following conditions? No	Yes
Myocardial Infarction	○	○
Hypertension	○	○
High blood cholesterol	○	○
Type I Diabetes	○	○
Type II Diabetes	○	○
Heart Failure	○	○
Stroke/Mini Stroke	○	○
Mental Illness ○ Depression	○	○
Mental Illness ○ Other (eg Bi-polar, schizophrenia)	○	○
Irregular Heart Beat / Atrial Fibrillation / Palpitations	○	○
Angina	○	○
Coronary Artery Disease	○	○
Vascular disease ○ Peripheral arterial disease	○	○
Vascular disease ○ Other - *Please specify*_____	○	○
Aneurysm *(Abdominal, thoracic)*	○	○
Heart Valve Condition	○	○
Pacemaker	○	○
Implanted Defibrillator	○	○
Renal Disease	○	○
Sleep Apnoea	○	○
Asthma / Lung Disease *(eg. Emphysema, COPD)*	○	○
Arthritis ○ Rheumatoid	○	○
Arthritis ○ Osteoarthritis	○	○
Eye disease / retinopathy	○	○
Migraine	○	○
Stomach ulcer	○	○
Cancer	○	○
Other serious condition Please specify _____	○	○

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Section 4 Blood test results

Blood chemistries

Date of test D D / M M / Y Y Y Y

Sodium	☐☐☐ mmol/L	Alkaline Phosphate Level	☐☐☐ mmol/L
Potassium	☐.☐ mmol/L	Calcium Level	☐.☐☐ mmol/L
Urea	☐☐.☐ mmol/L	Corrected Calcium Level	☐.☐☐ mmol/L
Creatinine	☐☐☐ umol/L	Magnesium	☐.☐☐ mmol/L
eGFR	☐☐☐	Phosphate	☐.☐☐ mmol/L
Total Bilirubin	☐☐☐ umol/L	C-Reactive protein	☐☐.☐☐ mg/L
Albumin	☐☐☐ g/L	Interleukin-6	☐☐.☐☐ ug/mL
ALT	☐☐☐ mmol/L	TNF-alpha	☐☐.☐☐ pg/mL
AST	☐☐☐ mmol/L	Vit D	☐☐.☐☐ nmol/L
GGT	☐☐☐ mmol/L		

Haematology results

Red blood cells	☐.☐ $x10^{12}/L$	Haemoglobin	☐☐☐ g/L
Haematocrit	☐.☐☐	White blood cells	☐.☐☐ $x10^{9}/L$
Platelets	☐☐☐ $x10^{9}/L$		

Coagulation studies

APTT	☐☐☐ sec	INR	☐.☐

Section 5 Echocardiography

Ejection Fraction ☐☐ %

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Section 6 Physical examination

Date of assessment D D / M M / Y Y Y Y

NYHA Class ◯ I ◯ II ◯ III ◯ IV

Height | | | cm

Weight | | | Kg

AKPS

◯ 100 = Normal; no complaints; no evidence of disease

◯ 90 = Able to carry on normal activity; minor signs or symptoms

◯ 80 = Normal activity with effort; some signs and symptoms of disease

◯ 70 = Cares for self; unable to carry on normal activity or to do active work

◯ 60 = Requires occasional assistance but is able to care for most his needs

◯ 50 = Requires condsiderable assistance and frequent medical care

◯ 40 = In bed more than 50% of time

◯ 30= Almost completely bedfast

◯ 20 = Totally bedfast and requring extensive nursing care by professionals and/or family

◯ 10= Comatose or barely rouseable

◯ 0 = Dead

Rhythm ◯ Sinus Rhythm ◯ Atrial Fibrillation ◯ Paced ◯ Other

Blood Pressure | | | / | | | mmHg

Hand grip strength

Right hand First | | Kg Second | | Kg Third | | Kg Average | | Kg

Left Hand First | | Kg Second | | Kg Third | | Kg Average | | Kg

5 metre walk test First | | Secs Second | | Secs Third | | Secs Average | | Secs

Section 7 Medications (on discharge)

◯ ACE inhibitor
◯ Angiotensin Receptor Blocker
◯ Beta blocker
◯ Digitalis
◯ Antiarrhythmic
◯ Nitrate
◯ Aldosterone antagonist
◯ Loop diuretic
◯ Other vasodilator
◯ Ivabradine
◯ Lipid lowering agent
◯ Antiplatelet
◯ Anticoagulant
◯ Thiazide diuretic
◯ Calcium channel antagonist

◯ Potassium
◯ Magnesium
◯ Calcium
◯ Iron tablets
◯ Fish oil
◯ Glucosamine
◯ Vitamin B
◯ Vitamin C
◯ Vitamin D

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Medication list (on discharge)

	Generic name	Route	Total Daily Dose	Unit
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				
9.				
10.				
11.				
12.				
13.				
14.				
15.				
16.				
17.				

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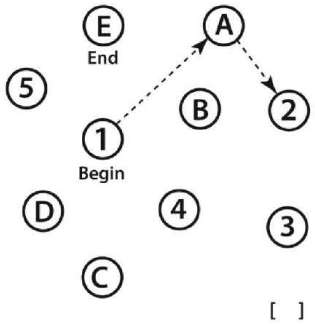
Section 8 MOCA

VISUOSPATIAL / EXECUTIVE



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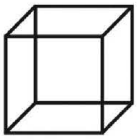
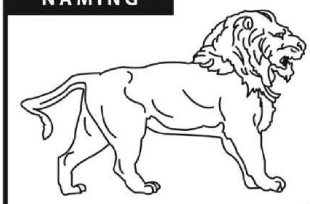


Copy cube [ ]

Draw CLOCK (Ten past eleven) (3 points) [ ] Contour [ ] Numbers [ ] Hands

POINTS __/5

NAMING



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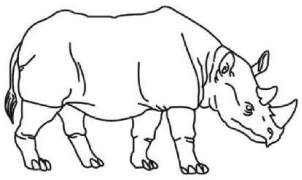
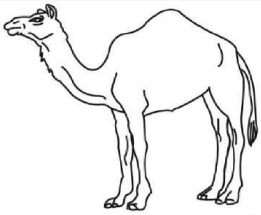


[ ]



[ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

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Section 9 Frailty (1)

Because of a health problem, do you have difficulty climbing one flight of stairs without resting? ○ No ○ Yes

What has your appetite been like?

○ Diminution and/or eating less than usual ○ No change in desire or eating the same as usual ○ Increase in desire and/or eating more than usual

Have you been eating more or less than usual? ○ Less ○ More

In the last month, have you had too little energy to do the things you wanted to do? ○ No ○ Yes

How often do you engage in activities that require a low or moderate level of energy such as gardening, cleaning the car, or going for a walk?

○ More than once a week ○ Once a week ○ One to three times a month ○ Hardly ever or never

In the last week, did you feel on at least 3 days, that you couldn't get going? ○ No ○ Yes

Have you, in the last 3 months, been eating more or less than usual? ○ Less ○ More

In the last year, have you developed decreased grip strength? ○ No ○ Yes

In the last year, have you lost more than 5 kgs unintentionally? ○ No ○ Yes

In the last week, did you feel on at least 3 days, that everything you did was an effort? ○ No ○ Yes

How often in the last week did feel that everything was an effort?

○ Rarely or none of the time (<1 day) ○ Some or little of the time (1-2 days) ○ A moderate amount of time (3-4 days) ○ Most of the time

In the last year, have you developed increasing fatigue/lethargy or declining endurance? ○ No ○ Yes

Because of a health problem, do you have difficulty [expected to last more than 3 months] walking 100 metres? ○ No ○ Yes

In the last year, have you developed a slower walking pace (over 5 metres) ○ No ○ Yes

How often in the last week did feel that you could not get going?

○ Rarely or none of the time (<1 day) ○ Some or little of the time (1-2 days) ○ A moderate amount of time (3-4 days) ○ Most of the time

In the last year, have you developed a decline in typical activity level ○ No ○ Yes

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In the past two weeks which activities have you done?

If the activity was done in the past two weeks:

		How often have you done the acitivity in the last two weeks?	What is the average amount of time that you spent per session?	How many months per year did you do the activity?
Walking for exercise?	○ No ○ Yes	# times	h h : m m	# months
Moderately strenuous chores (e.g. scrubbing, or vacuuming)?	○ No ○ Yes	# times	h h : m m	# months
Mowing the lawn?	○ No ○ Yes	# times	h h : m m	# months
Raking the lawn?	○ No ○ Yes	# times	h h : m m	# months
Gardening?	○ No ○ Yes	# times	h h : m m	# months
Hiking?	○ No ○ Yes	# times	h h : m m	# months
Jogging?	○ No ○ Yes	# times	h h : m m	# months
Biking?	○ No ○ Yes	# times	h h : m m	# months
Exercise cycle?	○ No ○ Yes	# times	h h : m m	# months
Dancing?	○ No ○ Yes	# times	h h : m m	# months
Aerobics/aerobic dance?	○ No ○ Yes	# times	h h : m m	# months
Bowling?	○ No ○ Yes	# times	h h : m m	# months
Golf?	○ No ○ Yes	# times	h h : m m	# months
Callsthenics/general exercise?	○ No ○ Yes	# times	h h : m m	# months
Swimming?	○ No ○ Yes	# times	h h : m m	# months

Have you done any other physical activities in the past two weeks in addition to those listed above?

If yes list what they were:

Other: _____ # times | | h h : m m # months | |

Other: _____ # times | | h h : m m # months | |

Other: _____ # times | | h h : m m # months | |

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Section 10 EQ5-D

By placing a tick in one box in each group below, please indicate which statements best desrcibe your health today.

Mobility

- 9.1 I have no problems in walking about ☐
- 9.2 I have slight problems in walking about ☐
- 9.3 I have moderate problems in walking about ☐
- 9.4 I have severe problems in walking about ☐
- 9.5 I am unable to walk about ☐

Please tick one box

Self-care

- 9.6 I have no problems washing or dressing myself ☐
- 9.7 I have slight problems washing or dressing myself ☐
- 9.8 I have moderate problems washing or dressing myself ☐
- 9.9 I have severe problems washing or dresing myself ☐
- 9.10 I am unable to wash or dress myself ☐

Please tick one box

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

- 9.11 I have no problems doing my usual activities ☐
- 9.12 have slight problems doing my usual activities ☐
- 9.13 I have moderate problems doing my usual activities ☐
- 9.14 I have severe problems doing my usual activities ☐
- 9.15 I am unable to do my usual activities ☐

Please tick one box

Pain/Discomfort

- 9.16 I have no pain or discomfort ☐
- 9.17 I have slight pain or discomfort ☐
- 9.18 I have moderate pain or discomfort ☐
- 9.19 I have severe pain or discomfort ☐
- 9.20 I have extreme pain or discomfort ☐

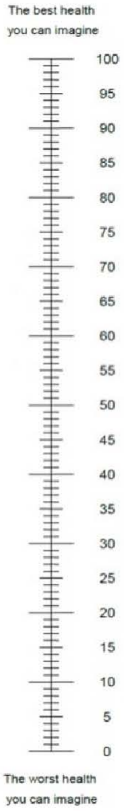
Please tick one box

Anxiety/Depression

- 9.21 I am not anxious or depressed ☐
- 9.22 I am slightly anxious or depressed ☐
- 9.23 I am moderately anxious or depressed ☐
- 9.24 I am severely anxious or depressed ☐
- 9.25 I am extremely anxios or depressed ☐

Please tick one box

Mark an **X** on the scale below to indicate how your health is TODAY



HEALTH STATE TODAY (number) = ☐

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Section 11 DMI

Please consider the following questions and rate how true each one is in relation to how you have been feeling **lately** (i.e. in the last two to three days) **compared to how you normally feel.**

Please choose the most relevant option

	Not True	Slightly True	Moderately True	Very True
1. Are you stewing over things?	○	○	○	○
2. Do you feel more vulnerable than usual?	○	○	○	○
3. Are you being self-critical and hard on yourself?	○	○	○	○
4. Are you feeling guilty about things in your life?	○	○	○	○
5. Do you find that nothing seems to be able to cheer you up?	○	○	○	○
6. Do you feel as if you have lost your core and essence?	○	○	○	○
7. Are you feeling depressed?	○	○	○	○
8. Do you feel less worthwhile?	○	○	○	○
9. Do you feel hopeless or helpless?	○	○	○	○
10. Do you feel more distant from other people?	○	○	○	○

FRailty meAsureMEnt in Heart Failure (FRAME-HF)

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Death Form

Instructions: Shade circles like this: ● Not like this: ∅ Please print in BLOCK STYLE in the boxes

Date of death D D / M M / Y Y Y Y

Location of death

- ○ Hospital
- ○ Home
- ○ Nursing home / hostel
- ○ Other (Please specify) _____

Cause of death

- ○ CV
- ○ Non-CV

If CV related, is it HF?

- ○ Yes
- ○ No

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Re-admission Form

Follow-up stage ◯ 7-14 day ◯ 3 month ◯ 6 month ◯ 9 month ◯ 12 month

Re-admission details

Have they been in hospital since the last study visit/assessment ◯ No ◯ Yes

Re-admission status ◯ ED only ◯ Elective Admission ◯ Non-elective admission

Date of Admission D D / M M / Y Y Y Y Date of Discharge D D / M M / Y Y Y Y

Cause of Admission ◯ CV ◯ Non-CV Hospital ______________

If CV related, is it HF? ◯ Yes ◯ No

Re-admission status ◯ ED only ◯ Elective Admission ◯ Non-elective admission

Date of Admission D D / M M / Y Y Y Y Date of Discharge D D / M M / Y Y Y Y

Cause of Admission ◯ CV ◯ Non-CV Hospital ______________

If CV related, is it HF? ◯ Yes ◯ No

Re-admission status ◯ ED only ◯ Elective Admission ◯ Non-elective admission

Date of Admission D D / M M / Y Y Y Y Date of Discharge D D / M M / Y Y Y Y

Cause of Admission ◯ CV ◯ Non-CV Hospital ______________

If CV related, is it HF? ◯ Yes ◯ No

Re-admission status ◯ ED only ◯ Elective Admission ◯ Non-elective admission

Date of Admission D D / M M / Y Y Y Y Date of Discharge D D / M M / Y Y Y Y

Cause of Admission ◯ CV ◯ Non-CV Hospital ______________

If CV related, is it HF? ◯ Yes ◯ No

Re-admission status ◯ ED only ◯ Elective Admission ◯ Non-elective admission

Date of Admission D D / M M / Y Y Y Y Date of Discharge D D / M M / Y Y Y Y

Cause of Admission ◯ CV ◯ Non-CV Hospital ______________

If CV related, is it HF? ◯ Yes ◯ No

Appendix 4: Ethics approval

St Vincent's Hospital

A facility of St Vincent's
& Mater Health Sydney

St Vincent's Hospital Sydney Ltd
ABN 77 054 038 872
390 Victoria Street
Darlinghurst NSW 2010
Australia

T + 61 2 8382 1111
F + 61 2 9332 4142
www.stvincents.com.au

9 June 2016

Prof Peter Macdonald
Heart Lung Clinic
St Vincent's Hospital
Darlinghurst NSW 2010

Dear Peter

SVH File Number: 16/061
Project Title: Assessment of validity, timing and proxy ratings of quality of life and frailty in patients with heart failure
HREC Reference Number: LNR/16/SVH/86

Thank you for submitting the above project for ethical and scientific review.

Based on the information you have provided and in accordance with the NHMRC National Statement 2007 and NSW Health Policy Directive PD2010_055 'Ethical and Scientific Review of Human Research in NSW Public Health Organisations', this project has been assessed as low/negligible risk and is therefore exempt from full HREC review.

St Vincent's Hospital HREC (EC00140) has been accredited by NSW Ministry of Health as a Lead HREC under the model for single ethical and scientific review and Certified by the NHMRC under the National Certification Scheme. This lead HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. No HREC members with a conflict of interest were present for review of this project.

This project meets the requirements of the National Statement on Ethical Conduct in Human Research. I am pleased to advise that the Committee at an Executive meeting on **7 June 2016** has granted ethical and scientific approval of the above **single centre** project.

You are reminded that this letter constitutes *ETHICAL* and *SCIENTIFIC* approval only. You must not commence this research project at a site until a completed Site Specific Assessment Form and associated documentation have been submitted to the site Research Governance Officer and Authorised. A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The project is approved to be conducted at **St Vincent's Hospital, Sydney**

If a new site(s) is to be added please inform the HREC in writing and submit a Site Specific Assessment Form (SSA) to the Research Governance Officer at the new site.

The following documents have been approved:

- Study Protocol, Version 1, dated 5 March 2016
- Participant Information Sheet and Consent Form – Clinician, Version 3.0, dated 11 May 2016
- Participant Information Sheet and Consent form – Patient, Version 3.0, dated 16 May 2016
- Clinician Questionnaire 1, Version 1, dated 16 March 2016
- Clinician Questionnaire 2, Version 1, dated 16 March 2016
- Clinical Research Form – demographic and clinical data, Version 1, dated 16 March 2016

- Combine Frailty scoring tool (including St Vincent's Hospital Frailty Assessment), Version 1, dated 16 March 2016

The Low and Negligible Risk Research Form (LNRF) reviewed by the HREC was LNRF **AU/6/5694214**

Please note the following conditions of approval:

- HREC approval is valid for **5 years** from the date of the HREC Executive Committee meeting and expires on **7 June 2021**. The Co-ordinating Investigator is required to notify the HREC 6 months prior to this date if the project is expected to extend beyond the original approval date at which time the HREC will advise of the requirements for ongoing approval of the study.
- The Co-ordinating Investigator will provide an Annual Progress Report beginning in **June 2017**, to the HREC as well as a Final Study Report at the completion of the project in the specified format.
- The Co-ordinating Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project and any complaints made by participants regarding the conduct of the project.
- Proposed changes to the research protocol, conduct of the research, or length of approval will be provided to the HREC Executive for review, in the specified format.
- The HREC Executive will be notified, giving reasons, if the project is discontinued before the expected date of completion.
- Investigators holding an academic appointment (including conjoint appointments) and students undertaking a project as part of a University course may also be required to notify the relevant University HREC of the project. Investigators and students are advised to contact the relevant HREC to seek advice regarding their requirements.

Please note that only an electronic copy of this letter will be provided, if you require the original signed letter please contact the Research Office and we will be happy to provide this.

Should you have any queries regarding this project please contact the Research Office, Ph: (02) 8382-4960 or by E-mail: SVHS.Research@svha.org.au. The HREC Terms of Reference, Standard Operating Procedures, *National Statement on Ethical Conduct in Human Research* (2007) and the *CPMP/ICH Note for Guidance on Good Clinical Practice* and standard forms are available on the Research Office web-site to be found at: https://svhs.org.au/home/research-education/research-office

Please quote **SVH File Number: 16/061** in all correspondence.

The HREC wishes you every success in your research.

Yours sincerely,

pp

Sarah Charlton
HREC Executive Officer
St Vincent's Hospital Research Office
Translational Research Centre, 97-105 Boundary Street

cc: Dr Phillip Newton
TRIM REF: D/2016/38948

UTS HREC Approval - ETH16-0593

Research.Ethics@uts.edu.au <Research.Ethics@uts.edu.au>

Thu 07/07/2016 12:24

To: Julee McDonagh <Julee.McDonagh@student.uts.edu.au>; Phillip Newton <Phillip.Newton@uts.edu.au>; Roslyn Prichard <Roslyn.Prichard@uts.edu.au>; Sunita Jha <Sunita.RJha@student.uts.edu.au>; Research Ethics <research.ethics@uts.edu.au>; Stephen Goodall <Stephen.Goodall@uts.edu.au>

Dear Applicant

[External Ratification: ST Vincent's Hospital Sydney – 16/061 – 07/06/2016 - 07/06/2021]

The UTS Human Research Ethics Expedited Review Committee have reviewed your application titled, "FRailty meAsureMEnt in heart failure (FRAME-HF)", and agreed that the application meets the requirements of the NHMRC National Statement on Ethical Conduct In Human Research (2007). I am pleased to inform you that your external ethics approval has been ratified.

Your approval number is UTS HREC REF NO. ETH16-0593
Approval will be for the period specified above and subject to the provision of annual reports and evidence of continued support from the above-named Committee.

Please note that the ethical conduct of research is an on-going process. The National Statement on Ethical Conduct in Research Involving Humans requires us to obtain a report about the progress of the research, and in particular about any changes to the research which may have ethical implications. This report form must be completed at least annually, and at the end of the project (if it takes more than a year). The Ethics Secretariat will contact you when it is time to complete your first report.

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

You should consider this your official letter of approval. If you require a hardcopy please contact Research.Ethics@uts.edu.au.

To access this application, please follow the URLs below:
* if accessing within the UTS network: https://rm.uts.edu.au
* if accessing outside of UTS network: https://remote.uts.edu.au , and click on "RM6 - ResearchMaster Enterprise" after logging in.

We value your feedback on the online ethics process. If you would like to provide feedback please go to: http://surveys.uts.edu.au/surveys/onlineethics/index.cfm

If you have any queries about your ethics approval, or require any amendments to your research in the future, please do not hesitate to contact Research.Ethics@uts.edu.au.

Yours sincerely,

Professor Marion Haas

Chairperson
UTS Human Research Ethics Committee
C/- Research & Innovation Office
University of Technology, Sydney
E: Research.Ethics@uts.edu.au

Appendix 5: Deficit Accumulation Index used in FRAME-HF

Deficit	Cut-points
1. Difficulty climbing a flight of stairs	Yes = 1 No = 0
2. Difficulty walking 100 metres	Yes = 1 No = 0
3. Decline in typical activity level	Yes = 1 No = 0
4. Developed a slower walking pace	Yes = 1 No = 0
5. Decline in appetite/ eating less than usual	Yes = 1 No = 0
6. NYHA class	Class II = 0.5 Class III & IV = 1 Class I = 0
7. AKPS score	70 - 100 = 0 , 50 - 60 = 0.5, < 50 = 1
8. Self-care (washing and dressing) problems	Yes = 1 No = 0
9. Mobility problems	Yes = 1 No = 0
10. More than five medications per day	Yes = 1 No = 0
11. Body Mass index	Underweight or obese = 1 Overweight = 0.5 Normal = 0
12. Mild cognitive impairment (MoCA score <26)	Yes = 1 No = 0
13. Depression (DMI-10 score >9)	Yes = 1 No = 0
14. Myocardial infarction	Yes = 1 No = 0
15. Coronary artery disease	Yes = 1 No = 0
16. Diabetes type I or II	Yes = 1 No = 0
17. Peripheral vascular disease/peripheral arterial	Yes = 1 No = 0
18. Heart valve condition	Yes = 1 No = 0
19. Lung disease/COPD	Yes = 1 No = 0
20. Hemiplegia	Yes = 1 No = 0
21. Cerebrovascular disease (CVA/Stroke)	Yes = 1 No = 0

22. Renal disease	Yes = 1 No = 0
23. Stomach Ulcer	Yes = 1 No = 0
24. Atrial fibrillation	Yes = 1 No = 0
25. History of liver disease	Yes = 1 No = 0
26. Hypertension	Yes = 1 No = 0
27. High cholesterol	Yes = 1 No = 0
28. History of dementia	Yes = 1 No = 0
29. History of Cancer	Yes = 1 No = 0
30. Anaemia (Hb < 120 for Women or Hb < 130 for Men)	Yes = 1 No = 0
31. Low Albumin	Yes = 1 No = 0
	Number of deficits/31